Supporting Information for

Asymmetric Total Synthesis of (+)-Ovafolinins A and B

Xianhe Fang, Lei Shen, Xiangdong Hu*

Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, China.

The corresponding author (X.H.): xiangdonghu@nwu.edu.cn

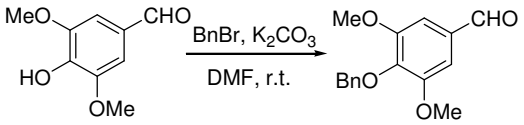
Contents

1. General information

Tetrahydrofuran (THF) and toluene were dried and distilled from sodium and benzophenone. Dichloromethane (CH_2Cl_2) was dried and distilled from calcium hydride. All commercial reagents and other solvents were used as received without further purification. Reactions were followed with TLC (254 nm silica gel 60-F plates); Visualization was accomplished with UV light. Flash chromatographies were carried out on silica gel 200-300 mesh. All NMR spectra were obtained at ambient temperature using Bruker-AVANCE III-400MHz spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ ^{1}H = 7.26 ppm, δ ^{13}C = 77.16 ppm) with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. 1H NMR data were recorded as follows: multiplicity (s = *singlet*, d = *doublet*, t = *triplet*, m = *multiplet* or *unresolved*, coupling constant in Hz, integration). The known products were characterized by comparing to the corresponding ^{1}H-NMR and ^{13}C-NMR from the literatures. High resolution mass spectrometry (HRMS) data were obtained on a Micro TOF-QⅡ (hybrid quadrupolar/time-of -flight) API US system by electrospray ionization (ESI) in the positive ion mode using a Bruker instrument. A Beijing Taike XT-4 microscopy melting point apparatus was used to measure the melting points of the compounds. Optical rotations were measured on a Rudolph Research Analytical Autopol II automatic polarimeter.

2. The synthesis of bromide 8

4-(benzyloxy)-3,5-dimethoxybenzaldehyde (11)

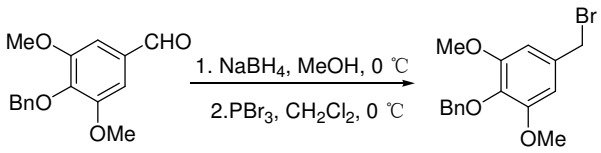


10 **11**

To a stirred solution of syringaldehyde **10** (10.0 g, 54.9 mmol, 1 eq.) in DMF (50 mL) at room temperature was added K_2CO_3 (9.1 g, 65.9 mmol, 1.2 eq.) and BnBr (9.8 g, 57.6 mmol, 1.2 eq.). After 36 h, the reaction was quenched with H_2O (200 mL) and extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with brine (3 x 200 mL) then dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel flash chromatography (silica gel, EtOAc/petroleum ether, 1:10) to afford **11** (13.7 g, 50.5 mmol, 92% yield) as a white solid.

TLC: R_f = 0.36 (silica gel, EtOAc/petroleum ether, 1:5).
Melting Point: 60-61 ℃.
^{1}H NMR (400 MHz; $CDCl_3$): δ 3.88 (s，6H), 5.12 (s, 2H), 7.10 (s, 2H), 7.28-7.35 (m, 3H), 7.46 (d, *J* = 6.6 Hz, 2H), 9.84 (s, 1H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$): δ 56.3, 75.1, 106.7, 182.1, 182.3, 182.5, 131.9, 137.3, 142.4, 154.0, 191.2 ppm.
HRMS (m/z): calculated for $C_{16}H_{16}NaO_4^+$ $[M+Na]^+$: 295.0941 , found 295.0943.

2-(benzyloxy)-5-(bromomethyl)-1,3-dimethoxybenzene (8)



11 **8**

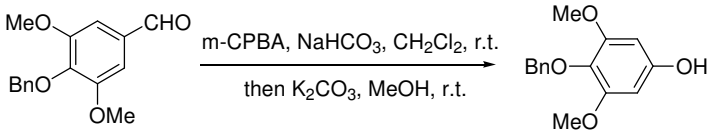
To a stirred solution of aldehyde **11** (8.00 g, 33.09 mmol, 1 eq.) in MeOH/DCM (2:1, 90 mL) was added $NaBH_4$ (1.25 g, 33.09 mmol, 1 eq.) at 0 ℃. The resulting mixture was stirred at room temperature for 1 h. The mixture was then quenched with acetone (10 mL) at 0 ℃ and stirred for 0.5 h. Solvent was removed under reduced pressure. To the residue was added ethyl acetate (60 mL) and H_2O (100 mL), then it was stirred vigorously for 1 h at room temperature. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was used directly without further purification.
The crude product was dissolved in DCM (100 mL). PBr_3 (7.94 g, 33.09 mmol, 1 eq.) was added at 0 °C. After stirred at 0 ℃ for 2h, the reaction was poured into ice water (150 mL) and the mixture was extracted with Et_2O (3 x 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (silica gel,

EtOAc/petroleum ether, 1:10) to afford bromide **8** (8.01 g, 23.82 mmol, 72% yield in 2 steps) as a white solid.

TLC: R_f = 0.54 (silica gel, EtOAc/petroleum ether, 1:5).
Melting Point: 57-58 ℃.
^{1}H NMR (400 MHz; $CDCl_3$): δ 3.82 (s, 6H), 4.45 (s, 2H), 4.99 (s, 2H), 6.60 (s, 2H), 7.28-7.36 (m, 3H), 7.47-7.49 (d, *J* = 7.5 Hz, 2H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$): δ 34.5, 56.2, 75.2, 106.3, 127.0, 128.3, 128.6, 133.4, 137.2, 137.8, 153.6 ppm.
HRMS (m/z): calculated for $C_{16}H_{17}BrNaO_3^+$ $[M+Na]^+$: 359.0253, found 359.0255.

3. The synthesis of phenol 5

4-(benzyloxy)-3,5-dimethoxyphenol (5)



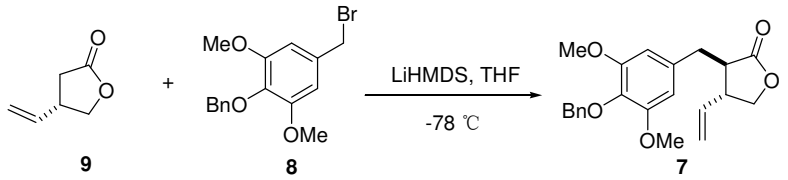
11 **5**

To a stirred solution of aldehyde **11** (4.0 g, 14.7 mmol, 1 eq.) in DCM (100 mL) at 0 ℃ was added *m*-CPBA (5.0 g, 29.4 mmol, 2 eq.) and $NaHCO_3$ (3.7 g, 44.1 mmol, 3 eq.). The resulting mixture was allowed warming to room temperature and stirred for 5 h. Solid was filtrated and washed with DCM (100 mL). The combined solvent was removed under reduced pressure. The residue was dissolved in MeOH (40 mL). KOH (2.5 g, 44.1 mmol, 3 eq.) was added. The mixture was stirred for 1 h. Solvent was removed under reduced pressure, water (100 mL) was added. The system was adjusted to pH=2 with 2*M* HCl and extracted with diethyl ether (3 x 50 mL). The organic extracts were combined, dried over Na_2SO_4 and solvent removed under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc/petroleum ether, 1:3) to give phenol **5** (2.7 g, 10.3 mmol, 70%) as a light yellow solid.

TLC: R_f = 0.50 (silica gel, EtOAc/petroleum ether, 1:1).
Melting Point: 117-118 ℃.
^{1}H NMR (400 MHz; $CDCl_3$): δ 3.63 (s, 6H), 4.91 (s, 2H), 5.99 (s, 2H), 7.24-7.32 (m, 3H), 7.45 (d, *J* = 6.6 Hz, 2H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$): δ 55.9, 75.6, 93.1, 128.0, 128.2, 128.8, 130.0, 137.6, 152.9, 153.9 ppm.
HRMS (m/z): calculated for $C_{15}H_{16}NaO_4^+$ $[M+Na]^+$: 283.0941, found 283.0946.

4. The synthesis of hemiacetal 14

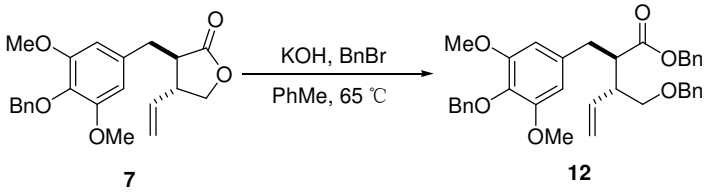
(3R,4R)-3-(4-(benzyloxy)-3,5-dimethoxybenzyl)-4-vinyl-dihydrofuran-2(3H)-one (7)



To a stirred solution of (S)-Taniguchi lactone **9** (200 mg, 1.78 mmol, 1 eq.) in THF (10 mL) at −78 ℃ was slowly added LiHMDS (1.0 M in THF, 2.14 mL, 2.14 mmol, 1.2 eq.). After stirring for 10 min at the same temperature, a solution of bromide **8** (720 mg, 2.14 mmol, 1.2 eq.) in THF (10 mL) was added in 5 min. The reaction mixture was allowed to slowly warm up, stirred for an additional 1h, then quenched by the addition of a saturated aqueous solution of NH_4Cl (0.25 mL). The organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether, 1:5) to afford lactone **7** (468 mg, 1.27 mmol, 71% yield, diastereoselectivity > 95 : 5) as a white solid.

TLC: R_f = 0.24 (silica gel, EtOAc/petroleum ether, 1:5).
Melting Point: 111 ℃.
^{1}H NMR (400 MHz; $CDCl_3$): δ 2.63–2.68 (m, 1H), 2.79-2.89 (m, 1H), 3.99 (ddd, *J* = 42.1, 14.1, 5.3 Hz, 1H), 3.78 (s, 3H), 3.85 (t, *J* = 9.5 Hz, 1H), 4.23 (t, *J* = 8.5 Hz, 1H), 4.99 (s, 2H), 5.09 (d, *J* = 11.1 Hz, 1H), 5.13 (d, *J* = 3.8 Hz, 1H), 5.58 (m, ddd, *J* = 16.9, 9.6, 7.5 Hz, 1H), 6.41 (s, 2H), 7.28-7.35 (m, 3H), 7.48 (d, *J* = 6.9 Hz, 2H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$): δ 33.7, 44.5, 46.6, 56.1, 69.9, 74.9, 106.5, 118.7, 127.8, 128.1, 128.5, 133.2, 135.1, 135.4, 137.8, 153.4, 177.8 ppm.
HRMS (m/z): calculated for $C_{22}H_{24}NaO_5^+$ $[M+Na]^+$: 391.1516, found 391.1505.
$[\alpha]_D^{25}$ = -17.2 (c=1.0, $CHCl_3$).

(2R,3R)-benzyl 2-(4-(benzyloxy)-3,5-dimethoxybenzyl)-3-(benzyloxymethyl)pent-4-enoate (12)

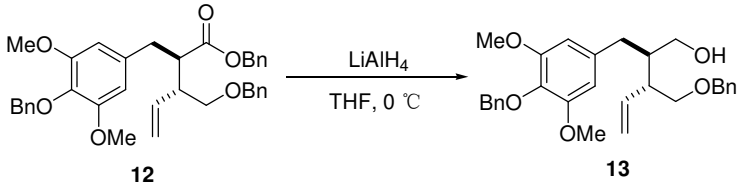


To a solution of **7** (420 mg, 1.14 mmol, 1 eq.) in toluene (7.0 mL) at room temperature was added KOH (320 mg, 5.71 mmol, 5 eq.) and BnBr (976 mg, 5.71 mmol, 5eq.). Then the flask was put into oil-bath pre-heated at 65 ℃. After 7 h, the reaction was quenched with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether, 1:10) to afford ester **12** (545 mg, 0.89 mmol, 78% yield) as a colorless oil.

TLC: R_f = 0.41 (silica gel, EtOAc/petroleum ether, 1:5).
^{1}H NMR (400 MHz; $CDCl_3$): δ 2.69-2.80 (m, 2H), 2.85-2.92 (m, 2H), 3.47 (d, *J* = 5.9 Hz, 2H), 3.69 (s,

6H), 4.41 (s, 2H), 4.87 (s, 2H), 4.95 (s, 2H), 5.19-5.21 (m, 2H), 5.75 (ddd, *J* = 17.0, 14.3, 8.2 Hz, 1H), 6.33 (s, 2H), 7.07-7.09 (m, 2H), 7.25-7.34 (m, 11H), 7.49 (d, *J* = 6.9 Hz, 2H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$): δ 36.6, 47.0, 49.1, 55.0, 66.1, 71.0, 73.1, 75.0, 105.7, 118.4, 127.6, 127.7, 127.8, 128.1, 128.2, 128.4, 128.5, 135.3, 135.8, 136.7, 138.0, 138.2, 153.3, 171.5 ppm.
HRMS (m/z): calculated for $C_{36}H_{38}NaO_6^+$ $[M+Na]^+$: 589.2561, found 589.2567.
$[\alpha]_D^{25}$ = +19.4 (c=1.0, $CHCl_3$).

(2R,3R)-2-(4-(benzyloxy)-3,5-dimethoxybenzyl)-3-(benzyloxymethyl)pent-4-en-1-ol (13)

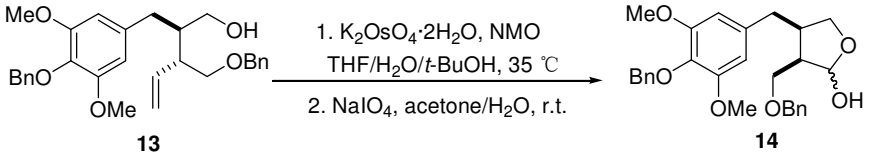


12 **13**

To a stirred solution of ester **12** (1.27 g, 1.78 mmol, 1 eq.) in THF (20 mL) at 0 ℃ was carefully added $LiAlH_4$ (128 mg, 2.14 mmol, 1.2 eq.). After stirring for 0.5 h at the same temperature, the reaction mixture was carefully quenched by the addition of H_2O (0.25 mL). Then aq. HCl (1*N*, 20 mL) and Et_2O (20 mL) were added and the solution was stirred for 0.5 h. The layers were separated and the aqueous phase was extracted with Et_2O (2 x 20 mL). The organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether, 1:4 to 1:2) to afford alcohol **13** (1.26 g, 1.76 mmol, 99% yield) as a white solid.

TLC: R_f = 0.37 (silica gel, EtOAc/petroleum ether, 1:2).
Melting Point: 59-60 ℃.
^{1}H NMR (400 MHz; $CDCl_3$): δ 1.88-1.93 (m, 1H), 2.44-2.58 (m, 3H), 2.70 (dd, *J* = 13.6, 4.5 Hz, 1H), 3.45 (dd, *J* = 11.4, 4.8 Hz 1H), 3.53-3.65 (m, 3H), 3.76 (s, 6H), 4.53 (dd, *J* = 17.2, 11.8, Hz 2H), 4.96 (s, 2 H), 5.15-5.27 (m, 2H), 5.79-5.88 (m, 1H), 6.36 (s, 2H), 7.24-7.34 (m, 8H), 7.48 (d, *J* = 6.9 Hz, 2H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$): δ 35.3, 44.9, 45.4, 56.1, 61.8, 71.9, 73.5, 75.1, 106.0, 117.3, 127.9, 128.2, 128.6, 135.0, 136.1, 137.7, 138.0, 138.2, 153.3 ppm.
HRMS (m/z): calculated for $C_{29}H_{34}NaO_5^+$ $[M+Na]^+$: 485.2298, found 485.2308.
$[\alpha]_D^{25}$ = +9.0 (c=1.0, $CHCl_3$).

(3R,4R)-4-(4-(benzyloxy)-3,5-dimethoxybenzyl)-3-(benzyloxymethyl)-tetrahydrofuran-2-ol (14)

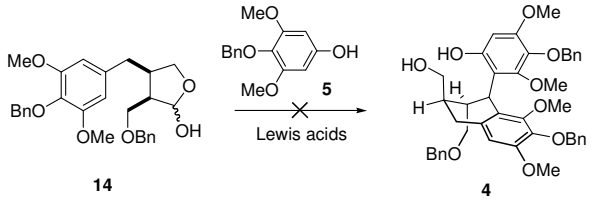


13 **14**

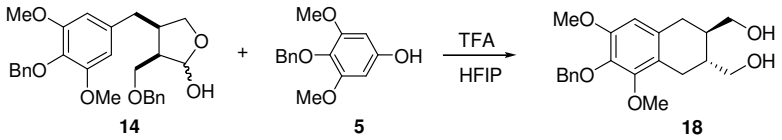
To a stirred solution of alcohol **13** (100 mg, 0.22 mmol, 1 eq.) in *t*-BuOH/H_2O/THF (1:1:1, 6 mL) was added $K_2OsO_4 \cdot H_2O$ (4 mg, 0.01 mmol) and NMO (50% aq. 152 mg, 0.66 mmol, 3 eq.). The resulting mixture was stirred at 35 ℃ for 2 days. The mixture was quenched with saturated aqueous Na_2SO_3 (4 mL)

and stirred for 1 h. The mixture was extracted with ethyl acetate (3 x 5 mL). The organic layers were combined and washed with aqueous KOH (1 *M*, 10 mL) then dried over Na_2SO_4. Solvent was removed under reduced pressure. The crude product was used directly in next step without further purification.
To a stirred solution of crude product in acetone/H_2O (3:1, 8 mL) was added $NaIO_4$ (139 mg, 0.66 mmol, 3 eq.) which was then stirred at room temperature for 0.5 h. The mixture was quenched with addition of brine (10 mL) and extracted with Et_2O (3 x 10 mL). The organic extracts were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether, 1:1) to afford hemiacetal **14** (94 mg, 0.20 mmol, 93% yield in 2 steps) as a colorless oil.

TLC: R_f = 0.41 (silica gel, EtOAc/petroleum ether, 1:1).
^{1}H NMR (400 MHz; $CDCl_3$ mixture of 2 diastereoisomers, signals of minor indicated by *): δ 2.39 (dd, *J* = 13.6, 10.5 Hz, 1H), 2.47-2.51 (m, 1H), 2.53-2.56* (m, 1H), 2.63-2.65* (m, 2H), 2.83-2.86* (m, 1H), 2.77 (dd, *J* = 13.6, 5.5 Hz, 1H), 2.87-2.93 (m, 1H), 3.52 (t, *J* = 8.6 Hz, 1H), 3.57-3.59* (m, 1H), 3.61-3.66 (m, 2H), 3.73-3.75* (m, 1H), 3.77 (s, 6H), 3.77* (s, 6H), 3.80-3.88 (m, 1H), 4.01 (t, *J* = 7.8 Hz, 1H), 4.54 (s, 1H), 4.56* (s, 2H), 4.97 (s, 2H), 5.46 (s, 1H), 5.51* (s, 1H), 6.33 (s, 2H), 6.34* (s, 2H), 7.25-7.36 (m, 12H), 7.48 (d, *J* = 7.1Hz, 3H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$ mixture of 2 diastereoisomers, signals of minor indicated by *): δ 34.0, 35.7*, 40.5*, 40.7, 46.2*, 49.2, 56.2, 66.7*, 67.4, 72.0, 73.5, 73.7*, 75.1, 99.3*, 101.4, 105.6, 105.8, 127.8, 127.9, 128.0, 128.2, 128.6, 135.4, 136.4, 136.9*, 138.0, 138.1, 153.5 ppm.
HRMS (m/z): calculated for $C_{28}H_{32}NaO_6^+$ $[M+Na]^+$: 487.2091, found 487.2091.



The initially proposed double Friedel-Crafts reaction process between **5** and **14** was checked in DCM with trifluoroacetic acid (TFA 2 eq.), $AlCl_3$ (2. eq.), $TiCl_4$ (2. eq.) and $BF_3{\cdot}OEt_2$, respectively. All experiments lead to complicated system. And no reasonable products were obtained after the column chromatography. As a note, the treatment of **5** and **14** with TFA in hexafluoroisopropanol (HFIP) gave an unexpected product **18** through an intramolecular Friedel-Crafts reaction/reduction/deprotection process.



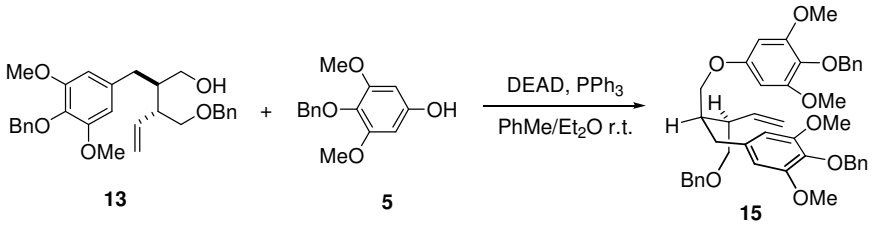
To a stirred solution of hemiacetal **14** (17 mg, 0.037 mmol, 1 eq.) in HFIP (0.5 mL), was added phenol **5** (17 mg, 0.073 mmol, 2 eq.) and TFA (4 mg, 0.073 mmol, 1 eq.). After 10 min at room temperature, the reaction was quenched with aq.$NaHCO_3$ (2 mL) and extracted with EtOAc (3 x 3 mL). The organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by

flash column chromatography (silica gel, EtOAc/petroleum ether, 1:1) to afford **18** (7 mg, 0.020 mmol, 53% yield) as a colorless oil and phenol **5** (15 mg).

TLC: R_f = 0.14 (silica gel, EtOAc/petroleum ether, 1:1).
^{1}H NMR (400 MHz; $CDCl_3$): δ 1.16-1.80 (m, 2H), 2.37 (dd, *J* = 16.6, 9.7 Hz, 1H), 2.59 (dd, *J* = 16.1, 9.8 Hz, 1H), 2.69 (dd, *J* = 16.1, 3.8 Hz, 1H), 2.81 (dd, *J* = 16.6, 4.2 Hz, 1H), 2.88 (s, 1H), 2.64-3.70 (m, 2H), 3.80 (s, 3H), 3.84-3.53 (m, 5H), 4.98 (s, 2H), 6.43 (s, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 2H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$): δ 26.4, 32.9, 40.0, 40.4, 56.1, 60.8, 66.2, 66.4, 75.4, 107.6, 122.1, 127.9, 128.3, 128.4, 132.1, 138.0, 139.2, 151.4, 151.8 ppm.
HRMS (m/z): calculated for $C_{21}H_{26}NaO_5^+$ $[M+Na]^+$: 381.1672, found 381.1690.
$[\alpha]_D^{25}$ = -36.4 (c=1.0, $CHCl_3$).

5. Total syntheses of (+)-ovafolinin B (2)

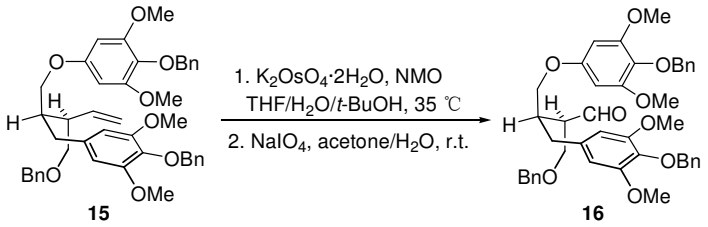
2-(benzyloxy)-5-((3R)-2-((4-(benzyloxy)-3,5-dimethoxyphenoxy)methyl)-3-(benzyloxymethyl)pent-4-enyl)-1,3-dimethoxybenzene (15)



To a stirred solution of alcohol **13** (100 mg, 0.32 mmol, 1 eq.) in toluene/Et_2O (4:1, 5 mL), was added PPh_3 (113 mg, 0.68 mmol, 2 eq.), phenol **5** (112 mg, 0.64 mmol, 2 eq.) and DIAD (87 mg, 0.68 mmol, 2 eq.). The resulting mixture was stirred for 18h at room temperature. Solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc/petroleum ether, 1:8) to give ether **15** (143 mg, 20.3 mmol, 94%) as a colorless oil.

TLC: R_f = 0.55 (silica gel, EtOAc/petroleum ether, 1:2).
^{1}H NMR (400 MHz; $CDCl_3$): δ 2.28-2.33 (m, 1H), 2.47-2.53 (m, 1H), 2.73-2.79 (m, 1H), 2.83 (dd, *J* = 13.6, 4.5 Hz, 1H), 3.58-3.64 (m, 2H), 3.65 (s, 6H), 3.74 (s, 1H), 3.76-3.82 (m, 2H), 5.17-5.24 (m, 2H), 5.87-5.96 (m, 1H), 6.04 (s, 1H), 6.33 (s, 1H), 7.27-7.35 (m, 11H), 7.46-7.48 (m, 4H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$): δ 34.9, 41.0, 44.7, 60.0, 56.2, 67.0, 71.7, 73.2, 75.1, 75.3, 92.3, 106.2, 117.7, 127.7, 127.8, 127.9, 128.2, 128.4, 128.5, 128.6, 131.2, 135.2, 136.4, 138.0, 138.1, 138.4, 153.4, 154.0, 155.8 ppm.
HRMS (m/z): calculated for $C_{44}H_{48}NaO_8^+$ $[M+Na]^+$: 727.3241, found 727.3242.
$[\alpha]_D^{25}$ = +36.6 (c=1.0, $CHCl_3$).

(2R)-3-((4-(benzyloxy)-3,5-dimethoxyphenoxy)methyl)-4-(4-(benzyloxy)-3,5-dimethoxyphenyl)-2-(benzyloxymethyl)butanal (16)



15 **16**

To a stirred solution of olefin **15** (0.95 g, 1.35 mmol, 1 eq.) in *t*-BuOH/H_2O/THF (1:1:1, 60 mL) was added $K_2OsO_4·H_2O$ (25 mg, 0.07 mmol) and NMO (50% aq. 0.93 g, 4.05 mmol, 3 eq.). The resulting mixture was stirred at 35 ℃ for 2 days. The mixture was quenched with saturated aqueous Na_2SO_3 (40 mL) and stirred for 1 h. The mixture was extracted with ethyl acetate (3 x 40 mL). The organic layers were combined and washed with aqueous KOH (1 M, 40 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure. The crude product was used directly in next step without further purification.

To a stirred solution of crude product in acetone/H_2O (3:1, 40 mL) was added $NaIO_4$ (0.85 g, 4.05 mmol, 3 eq.) and stirred for 1 h at room temperature. The mixture was quenched with addition of brine (20 mL) and extracted with Et_2O (3 x 40 mL). The organic extracts were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether, 1:5) to afford aldehyde **14** (734 mg, 1.04 mmol, 77% yield in 2 steps) as a colorless oil.

TLC: R_f = 0.45 (silica gel, EtOAc/petroleum ether, 1:2).

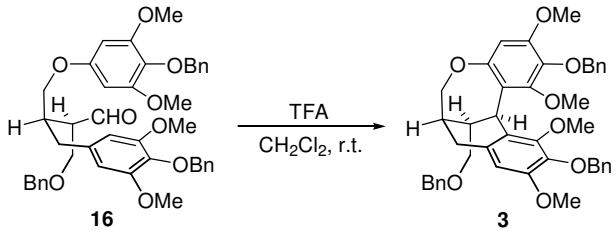
^{1}H NMR (400 MHz; $CDCl_3$): δ 2.70-2.74 (m, 1H), 2.78-2.84 (m, 3H), 3.68 (s, 6H), 3.76 (s, 6H), 3.83 (d, *J* = 4.3 Hz, 2H), 3.85-3.92 (m, 2H), 4.52 (s, 2H), 4.92 (s, 2H), 4.96 (s, 2H), 6.05 (s, 2H), 6.36 (s, 2H), 7.27-7.37 (m, 11H), 7.46-7.49 (m, 4H), 9.85 (d, *J* = 0.9 Hz, 1H) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 35.8, 38.6, 53.0, 55.9, 56.1, 66.4, 67.1, 73.5, 75.0, 75.3, 92.0, 106.1, 127.7, 127.8, 127.9, 128.1, 128.5, 128.6, 137.6, 137.7, 153.4, 153.9, 155.3, 203.5 ppm.

HRMS (m/z): calculated for $C_{43}H_{46}NaO_9^+$ $[M+Na]^+$: 729.3034, found 729.3036.

$[\alpha]_D^{25}$ = +21.6 (c=1.0, $CHCl_3$).

(13R,14R)-2,11-bis(benzyloxy)-14-((benzyloxy)methyl)-1,3,10,12-tetramethoxy-6,7,8,13-tetrahydro-7, 13-methanodibenzo[b,e]oxonine (3)



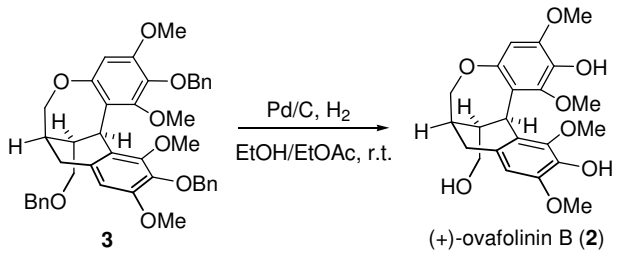
16 **3**

To a stirred solution of **16** (26 mg, 0.04 mmol, 1 eq.) in DCM (1 mL) was added TFA (4 mg, 0.68 mmol, 4 eq.). The resulting mixture was stirred for 1h at room temperature. The mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL) and extracted with ethyl acetate (3 x 4 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether=1:10) to afford **3** (22 mg, 0.03 mmol,

87% yield) as a colorless oil.

TLC: R_f = 0.57 (silica gel, EtOAc/petroleum ether, 1:2).
^{1}H NMR (400 MHz; $CDCl_3$): δ 2.35 (d, *J* = 6.3 Hz, 1H), 2.40 (t, *J* = 7.6 Hz, 1H), 2.91 (d, *J* = 17.6 Hz, 1H), 3.10 (dd, *J* = 17.5, 7.1 Hz, 1H), 3.40 (s, 3H), 3.49 (t, *J* = 8.8 Hz, 1H), 3.62 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.70 (s, 3H), 3.78 (s, 3H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.97 (s, 3H), 4.45 (dd, *J* = 12.1 2.6 Hz, 1H), 4.52 (dd, *J* = 22.7, 11.9 Hz, 2H), 4.64 (s, 1H), 4.86 (d, *J* = 10.8 Hz, 2H), 4.95 (d, *J* = 12.6 Hz, 2H), 5.06 (d, *J* = 10.7 Hz, 2H), 6.27 (s, 1H), 6.42 (s, 1H), 7.23-7.25 (m, 1H), 7.27-7.38 (m, 10H), 7.43 (d, *J* = 7.0 Hz, 2H), 7.54 (d, *J* = 4.7 Hz, 2H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$): δ 29.6, 30.6, 33.9, 41.2, 55.8, 55.9, 60.4, 62.1, 72.5, 73.3, 74.9, 75.3, 80.3, 101.8, 106.5, 122.9, 124.4, 127.6, 127.7, 127.9, 128.3, 128.4, 131.2, 137.6, 138.1, 138.6, 139.2, 151.6, 151.9, 152.0, 152.3, 156.4 ppm.
HRMS (m/z): calculated for $C_{43}H_{44}NaO_8^+$ $[M+Na]^+$: 711.2928, found 911.2927.
$[\alpha]_D^{25}$ = +137.2 (c=1.0, $CHCl_3$).

(+)-ovafolinin B (2)

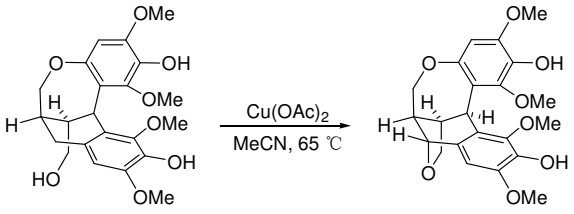


A mixture of **3** (311 mg, 0.45 mmol, 1 eq.) and 10% Pd/C (50% wetted, 40 mg) in EtOAc/EtOH (1:2, 15 mL) was evacuated and back-filled with H_2 three times. After stirring for 12 h at room temperature, the mixture was filtered over a pad of Celite and eluted with EtOAc(15 mL). The solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, MeOH/DCM, 1:20) to provide (+)-ovafolinin B (187 mg, 0.45 mmol, 99% yield) as a colorless amorphous.

TLC: R_f = 0.24 (silica gel, MeOH/DCM, 1:20).
^{1}H NMR (400 MHz; $CDCl_3$): δ 2.18–2.21 (m, 2H), 2.86 (d, *J* = 17.4 Hz, 1H), 3.03 (dd, *J* = 17.4, 6.9 Hz, 1H), 3.39 (s, 3H), 3.59 (dd, *J* = 10.6, 6.9 Hz, 1H), 3.69 (dd, *J* = 10.6, 7.9 Hz, 1H), 3.71 (s, 3H), 3.78 (br d, *J* = 11.4 Hz, 1H), 3.78 (s, 3H), 3.92 (s, 3H), 4.40 (dd, *J* = 12.0, 2.4 Hz, 1H), 4.58 (br s, 1H), 5.71 (s, 1H), 5.58 (s, 1H), 6.24 (s, 1H), 6.37 (s, 1H) ppm.
^{13}C NMR (100 MHz; $CDCl_3$): δ 29.2, 29.9, 33.9, 43.4, 55.8, 56.0, 59.8, 61.7, 64.8, 80.4, 101.2, 105.5, 122.4, 123.8, 126.2, 134.7, 136.4, 144.6, 145.3, 146.2, 152.9 ppm.
HRMS (m/z): calculated for $C_{22}H_{26}NaO_8^+$ $[M+Na]^+$: 441.1520, found 441.1516.
$[\alpha]_D^{17}$ = +166.0 (c=0.16, MeOH).

6. Total syntheses of (+)-ovafolinin A (1)

(+)-ovafolinin A (1)



(+)-ovafolinin B (**2**) (+)-ovafolinin A (**1**)

To a solution of (+)-ovafolinin B (**2**) (20 mg, 0.05 mmol, 1 eq.) in MeCN (2 mL) was added $Cu(OAc)_2$ (113 mg, 0.10 mmol, 2eq.). The resulting mixture was stirred for 2h at 65 ℃. The mixture was cold to room temperature and added Na_2EDTA (4 mL). After stirring for 0.5 h, the mixture was extracted with ethyl acetate (3 x 4 mL). The organic layers were combined and dried over Na_2SO_4 then concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, MeOH/DCM, 1:40) to afford (+)-ovafolinin A (**1**) (18.4 mg, 0.04 mmol, 91% yield) as a colorless amorphous.

TLC: R_f = 0.37 (silica gel, MeOH/DCM, 1:20).

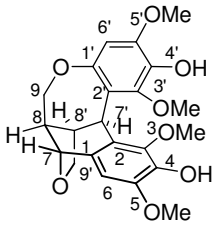
^{1}H NMR (400 MHz; $CDCl_3$): δ 2.31-2.35 (m, 1H), 2.59-2.62 (m, 1H), 3.24 (s, 1H), 3.74 (br d, *J* = 8.6 Hz, 1H), 3.77 (s, 3H), 3.86 (s, 3H), 3.99 (dd, *J* = 13.2, 2.82 Hz, 1H), 4.06 (s, 3H), 4.14 (dd, *J* = 8.5, 5.7 Hz, 1H), 4.50 (d, *J* = 2.4 Hz, 1H), 4.53 (d, *J* = 13.4 Hz, 1H), 4.76 (d, *J* = 4.4 Hz, 1H), 5.47 (s, 1H), 5.49 (s, 1H), 6.26 (s, 1H), 6.53 (s, 1H) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 37.5, 39.9, 43.1, 56.0, 56.2, 59.3, 60.7, 69.5, 72.6, 79.2, 100.9, 104.9, 123.0, 124.7, 128.9, 135.2, 138.7, 144.1, 145.1, 145.8, 146.3, 152.1 ppm.

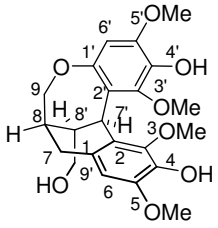
HRMS (m/z): calculated for $C_{22}H_{24}NaO_8^+$ $[M+Na]^+$: 439.1363, found 439.1362.

$[\alpha]_D^{22}$ = +159.4 (c=0.36, MeOH).

7. Comparison of ^{1}H NMR data of synthetic and natural ovafolinin A and B in $CDCl_3$



ovafolinin A (**1**)

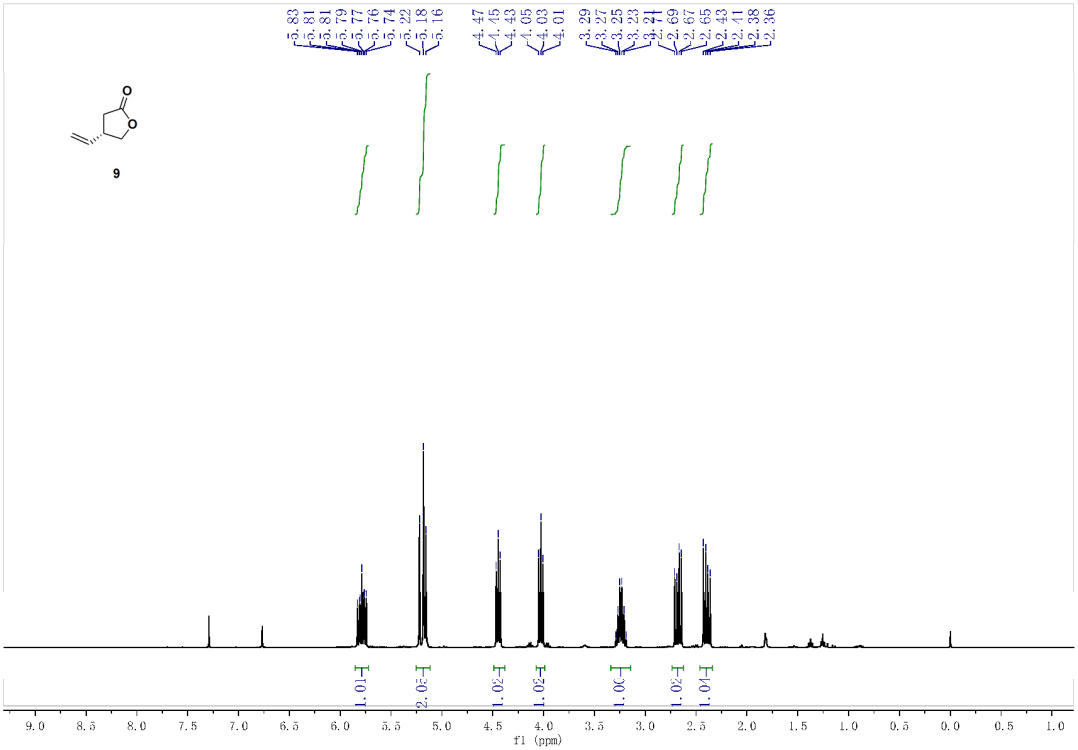


ovafolinin B (**2**)

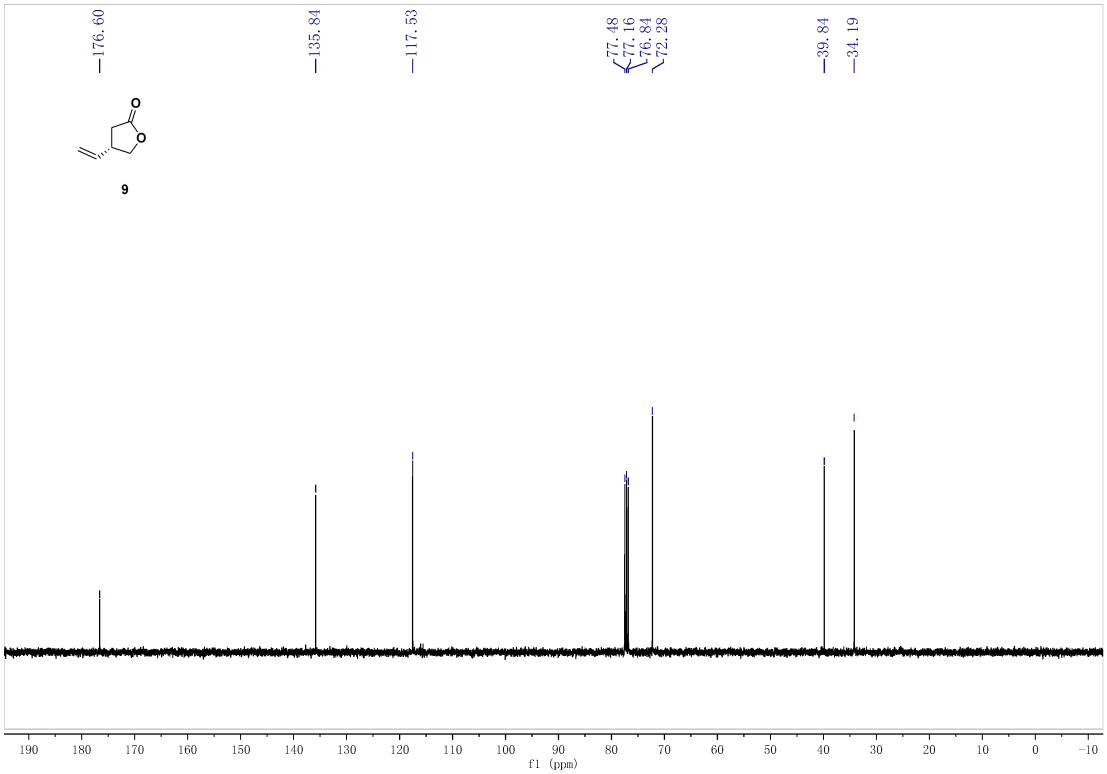
H	ovafolinin A natural	ovafolinin A synthetic	ovafolinin B natural	ovafolinin B synthetic
6	6.52 (1H, s)	6.53 (1H, s)	6.38 (1H, s)	6.37 (1H, s)
7	4.75 (1H, br d, 4.4)	4.76 (1H, d, 4.4)	2.86 (1H, br d, 17.4) 3.03 (1H, dd, 7.1, 17.4)	2.86 (1 H, d, 17.4) 3.03 (1 H, dd, 6.9, 17.4)
8	2.32 (1H, *)	2.31-2.35 (1H, m)	2.24 (1H, *)	2.18-2.21(1H, m)
9	3.96(1H, dd, 2.8, 13.3) 4.51 (1H, *br d, 13.3)	3.99 (1H, dd, 2.8, 13.2) 4.53 (1H, d, 13.4)	3.82 (1H, *) 4.41 (1H, dd, 2.7, 12.1)	3.78 (1H, br d, 11.4) 4.40 (1 H, dd, 2.4, 12.0)
6'	6.26(1H,s)	6.26 (1H, s)	6.25 (1H, s)	6.24 (1 H, s)
7'	4.49 (1H, d, 2.3)	4.50 (1H, d, 2.4)	4.59 (1H, br s)	4.58 (1 H, br s)
8'	2.60 (1H, *)	2.59-2.62 (1H, m)	2.22 (1H, *)	2.18-2.21(1H, m)
9'	3.73 (1H, br d, 8.5) 4.11 (1H, dd, 2.7, 8.5)	3.74 (1H, br d, 8.6) 4.14 (1H, dd, 5.7, 8.5)	3.62 (1H, dd, 7.1, 10.6) 3.72 (1H, *)	3.59 (1H, dd, 6.9, 10.6) 3.69 (1H, dd, 7.9, 10.6)
3-OMe	4.06 (3H, s)	4.06 (3H, s)	4.06 (3H, s)	3.92 (3H, s)
4-OH		5.49 (1H, s)		5.58 (1 H, s)
5-OMe	3.86 (3H, s)	3.86 (3H, s)	3.81 (3H, s)	3.78 (3H, s)
3'-OMe	3.77 (3H, s)	3.77 (3H, s)	3.74 (3H, s)	3.71 (3H, s)
4'-OH		5.47 (1H, s)		5.71 (1H, s)
5'-OMe	3.23 (3H, s)	3.24 (3H, s)	3.42 (3H, s)	3.39 (3H, s)

8. Copies of ^{1}H NMR and ^{13}C NMR Spectra

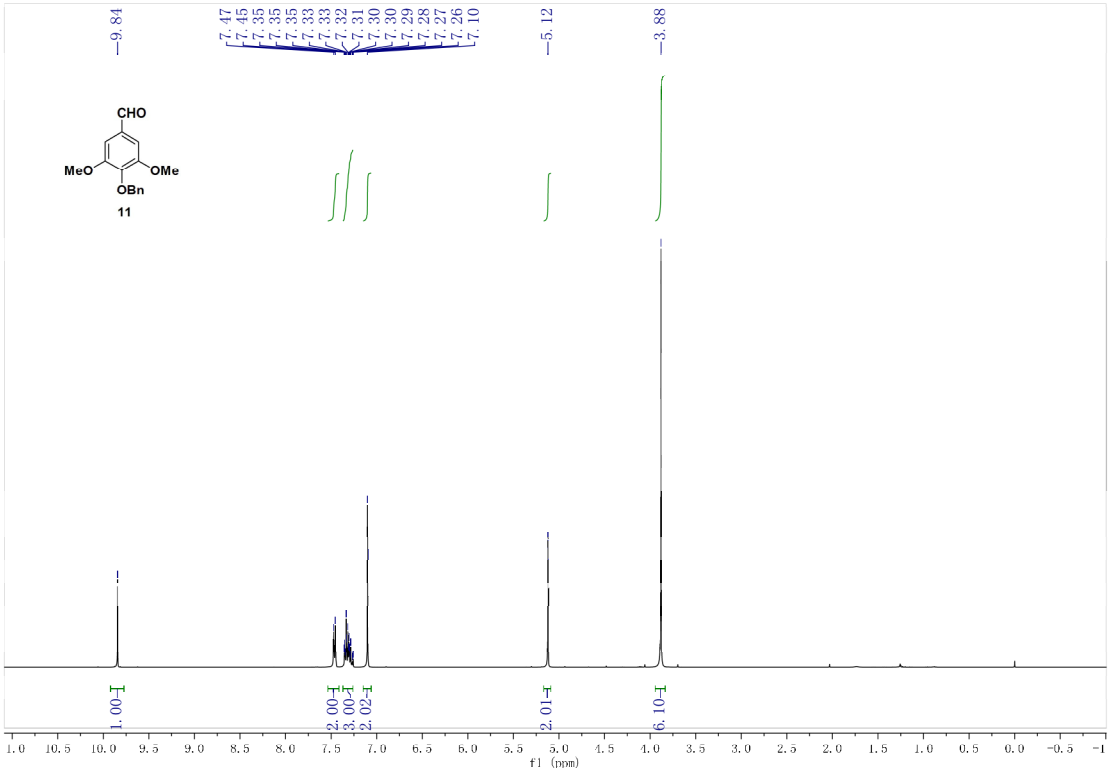
Copy of ^{1}H NMR spectrum of compound **9**



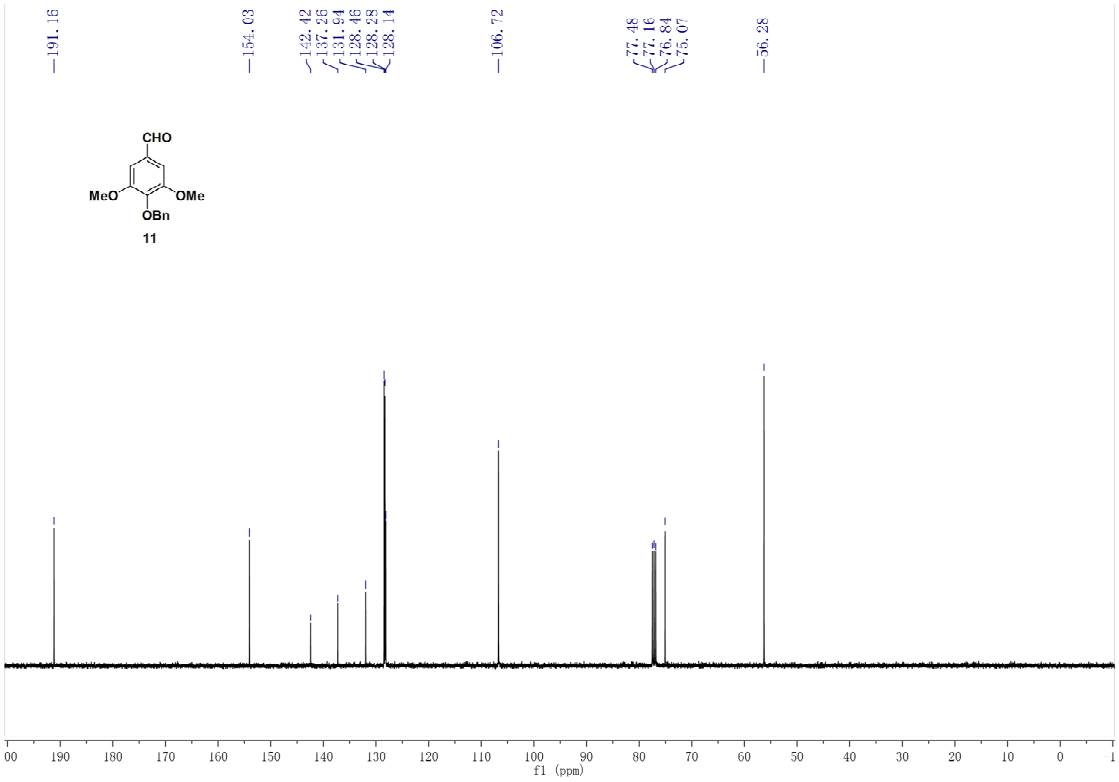
Copy of ^{13}C NMR spectrum of compound **9**



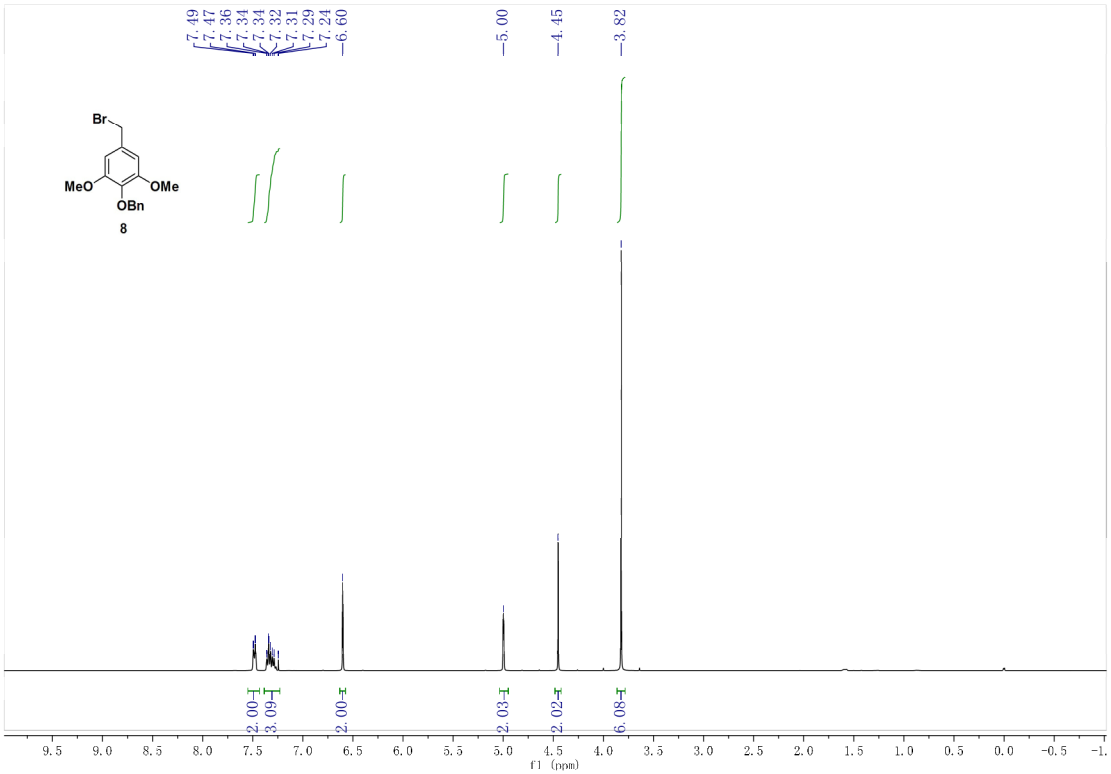
Copy of ^{1}H NMR spectrum of compound **11**



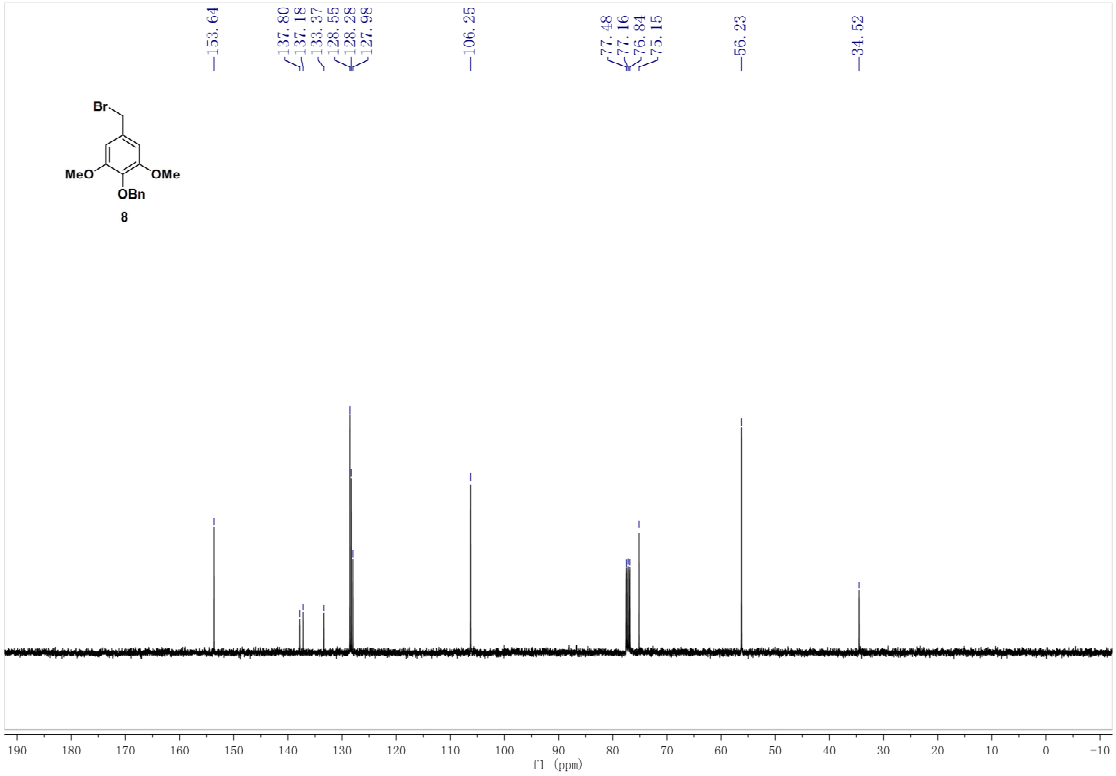
Copy of ^{13}C NMR spectrum of compound **11**



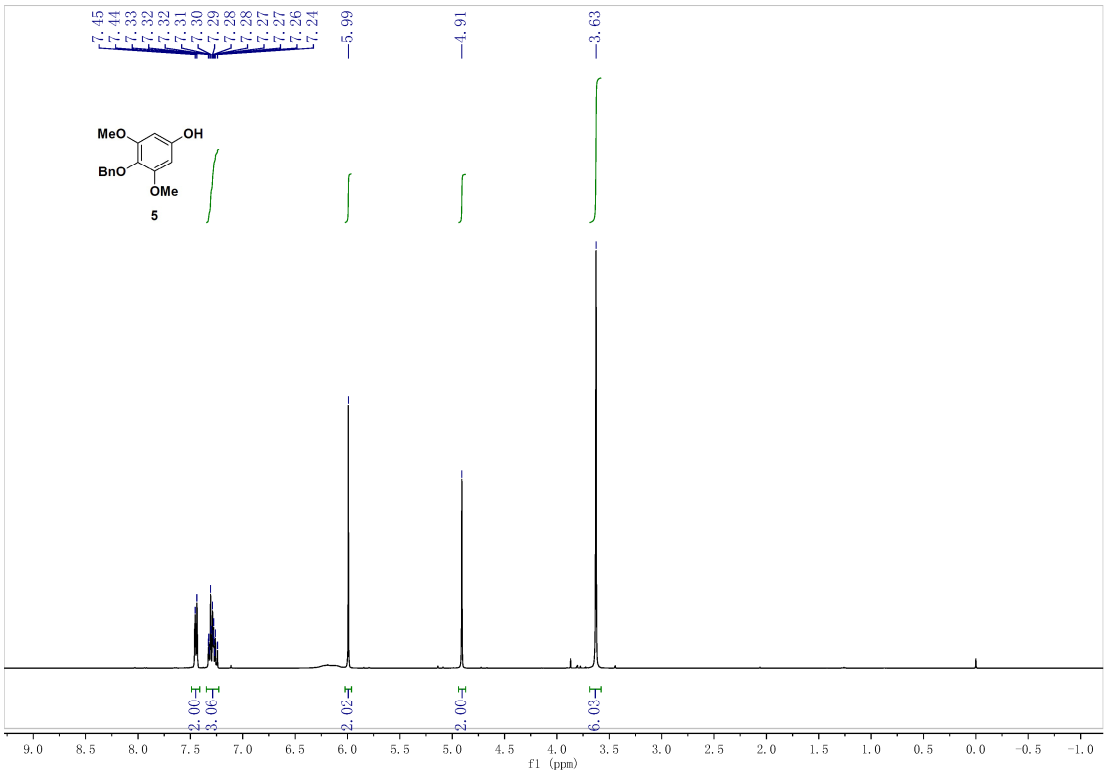
Copy of ^{1}H NMR spectrum of compound **8**



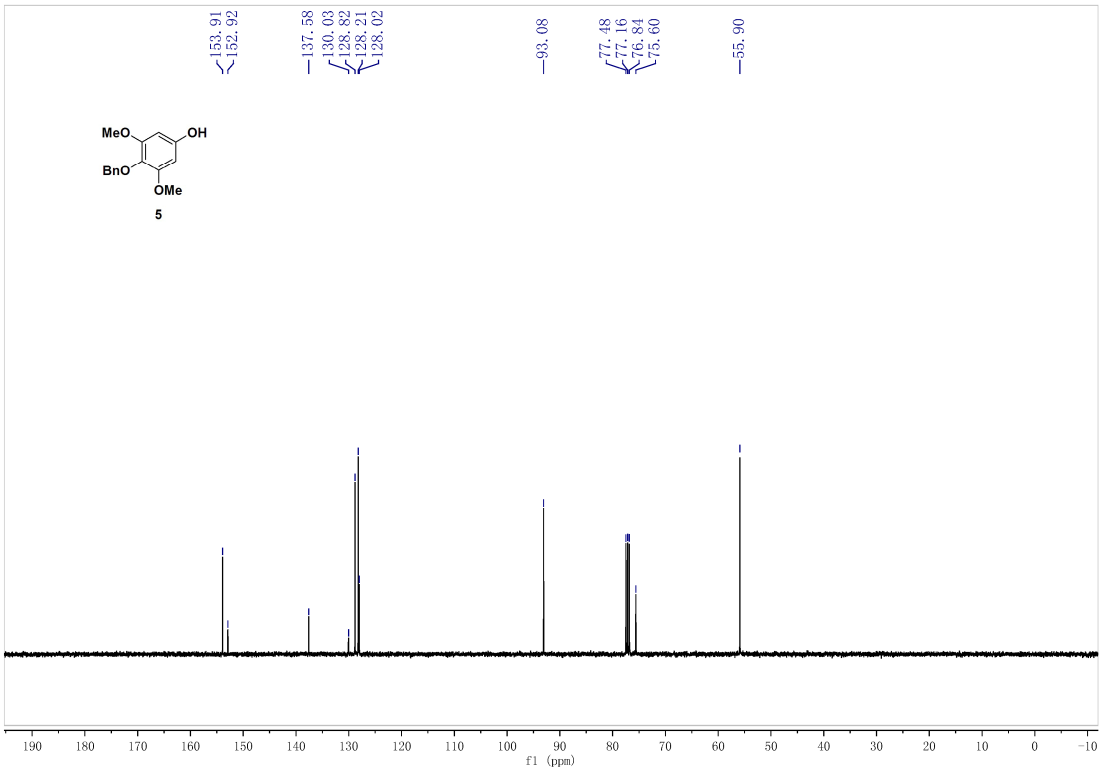
Copy of ^{13}C NMR spectrum of compound **8**



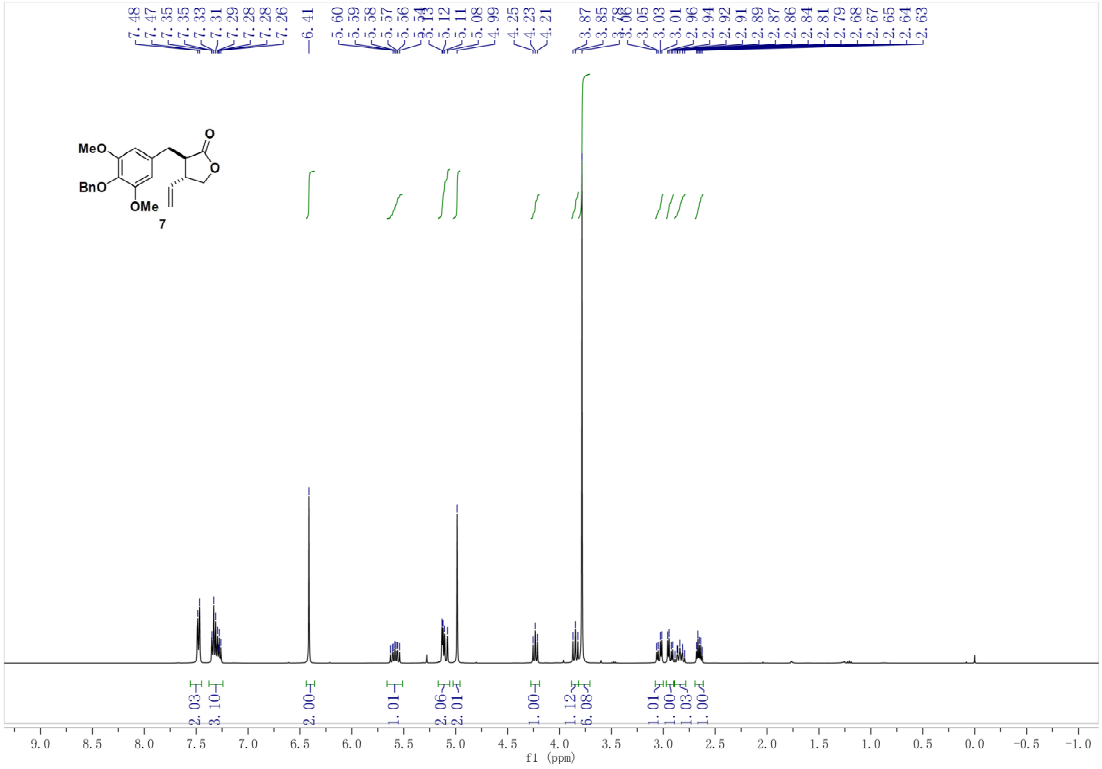
Copy of ^{1}H NMR spectrum of compound **5**



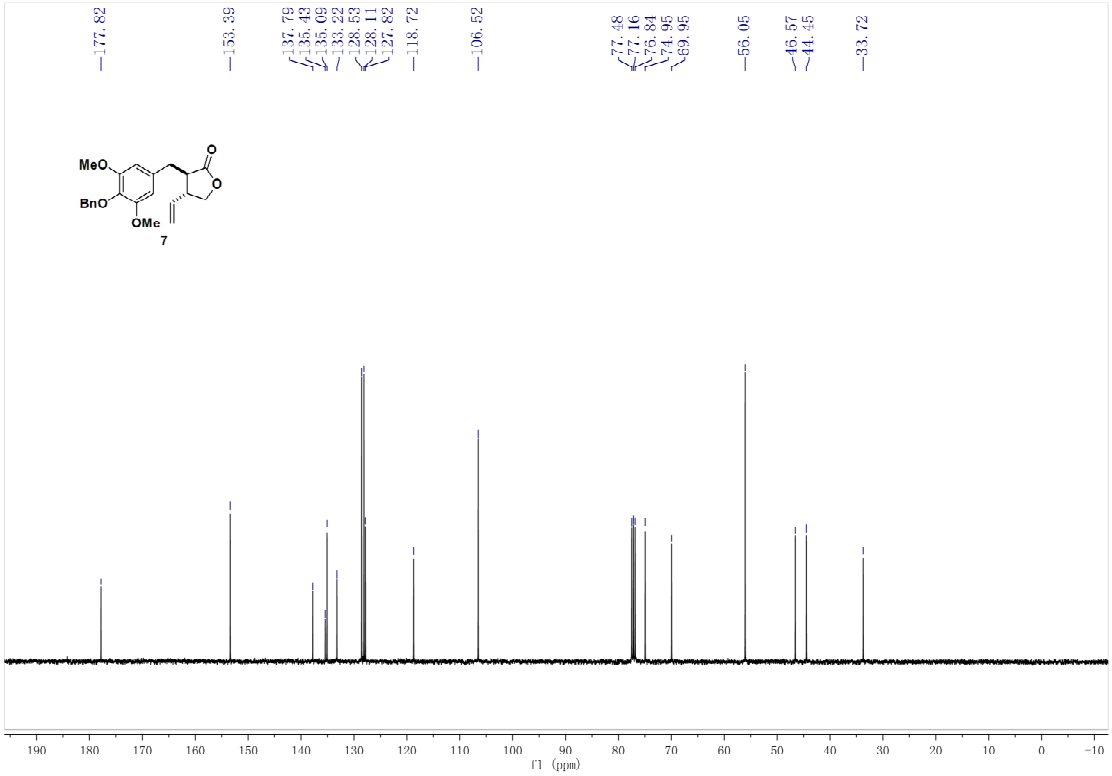
Copy of ^{13}C NMR spectrum of compound **5**



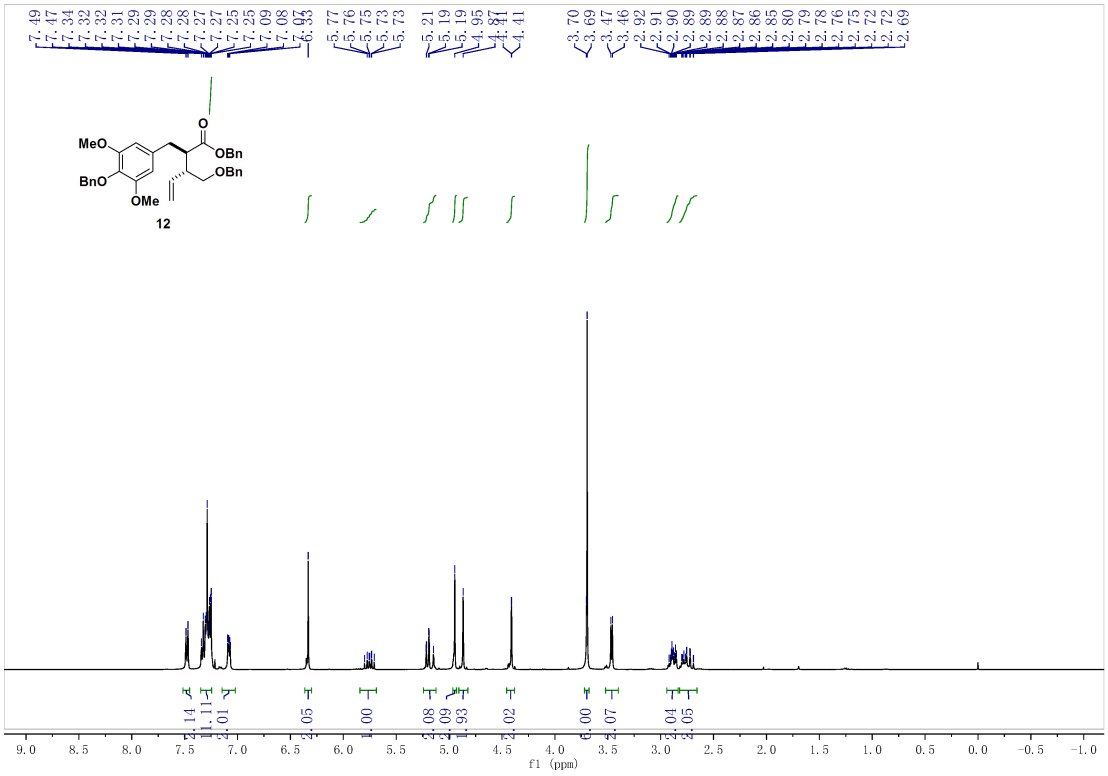
Copy of ^{1}H NMR spectrum of compound **7**



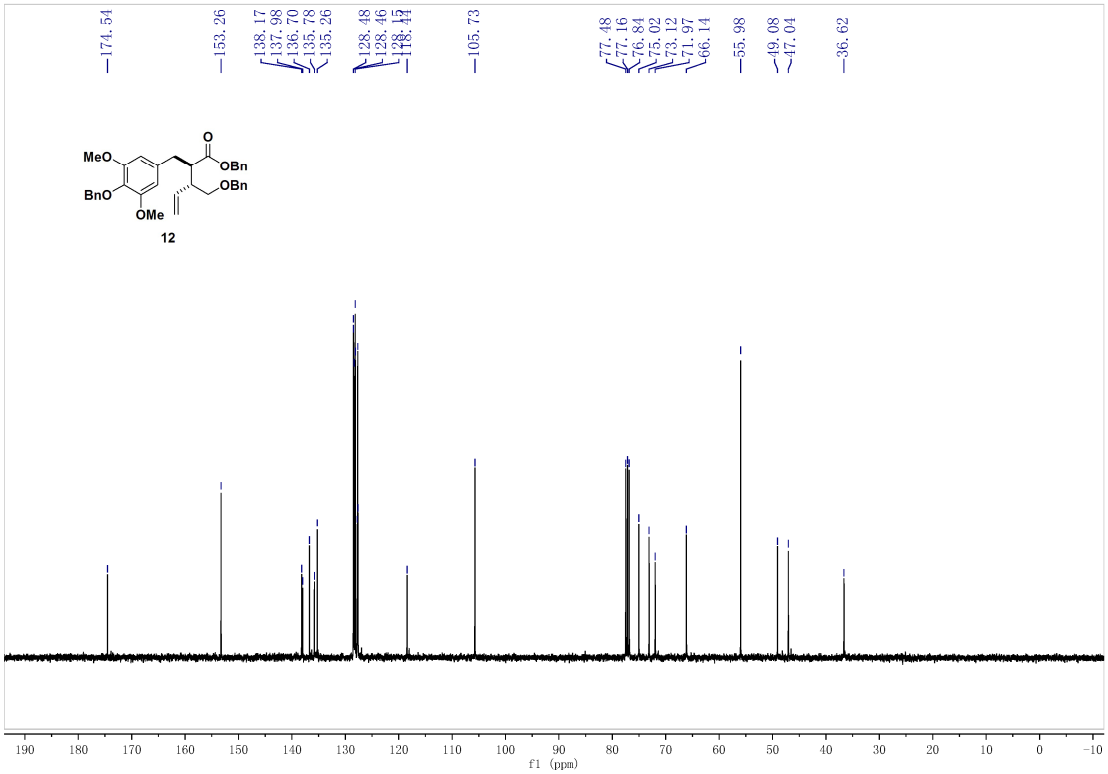
Copy of ^{13}C NMR spectrum of compound **7**



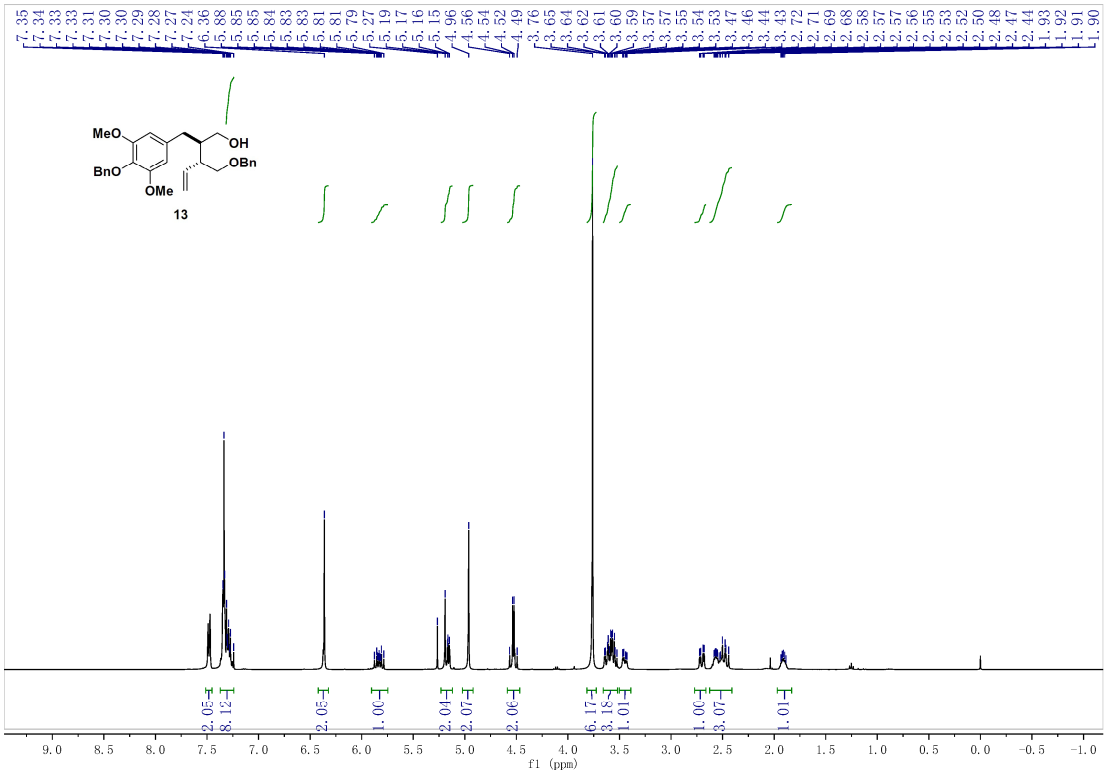
Copy of ^{1}H NMR spectrum of compound **12**



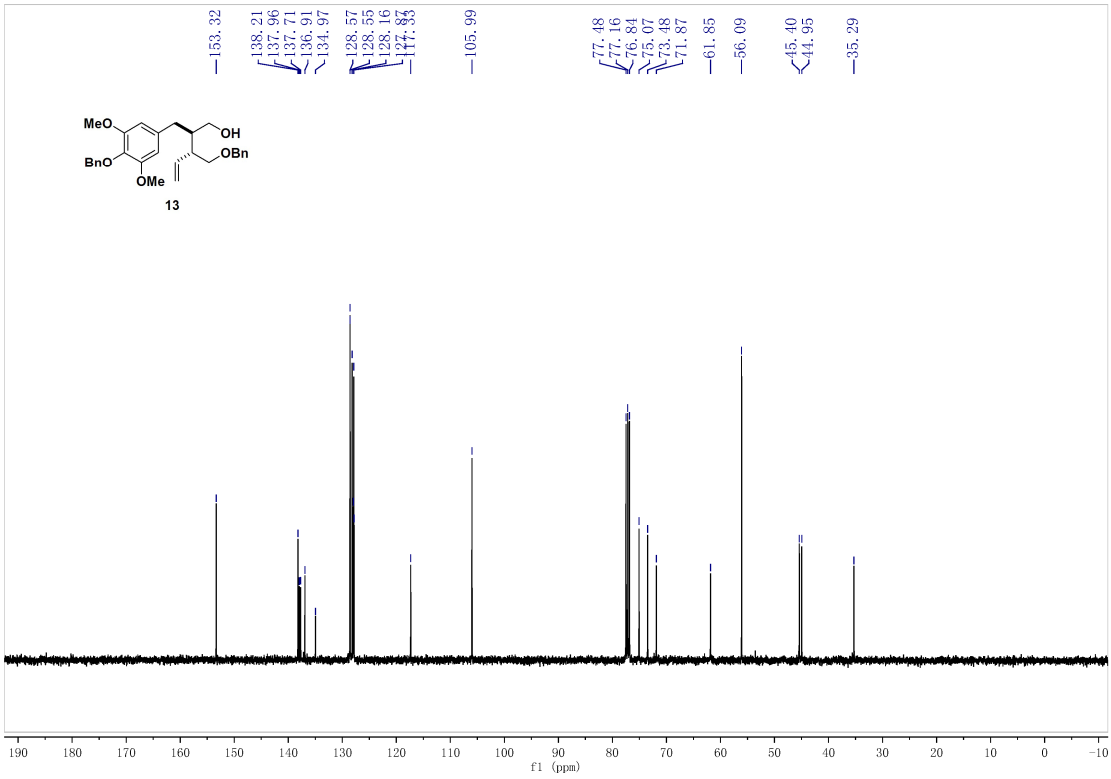
Copy of ^{13}C NMR spectrum of compound **12**



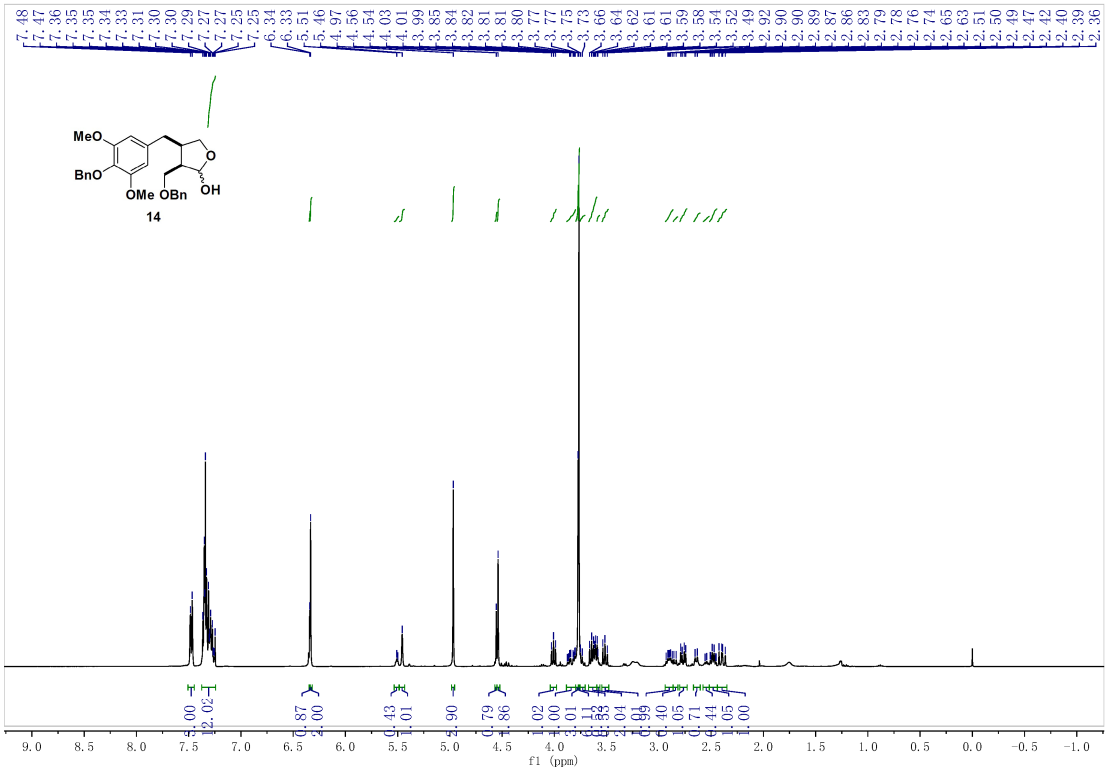
Copy of ^{1}H NMR spectrum of compound **13**



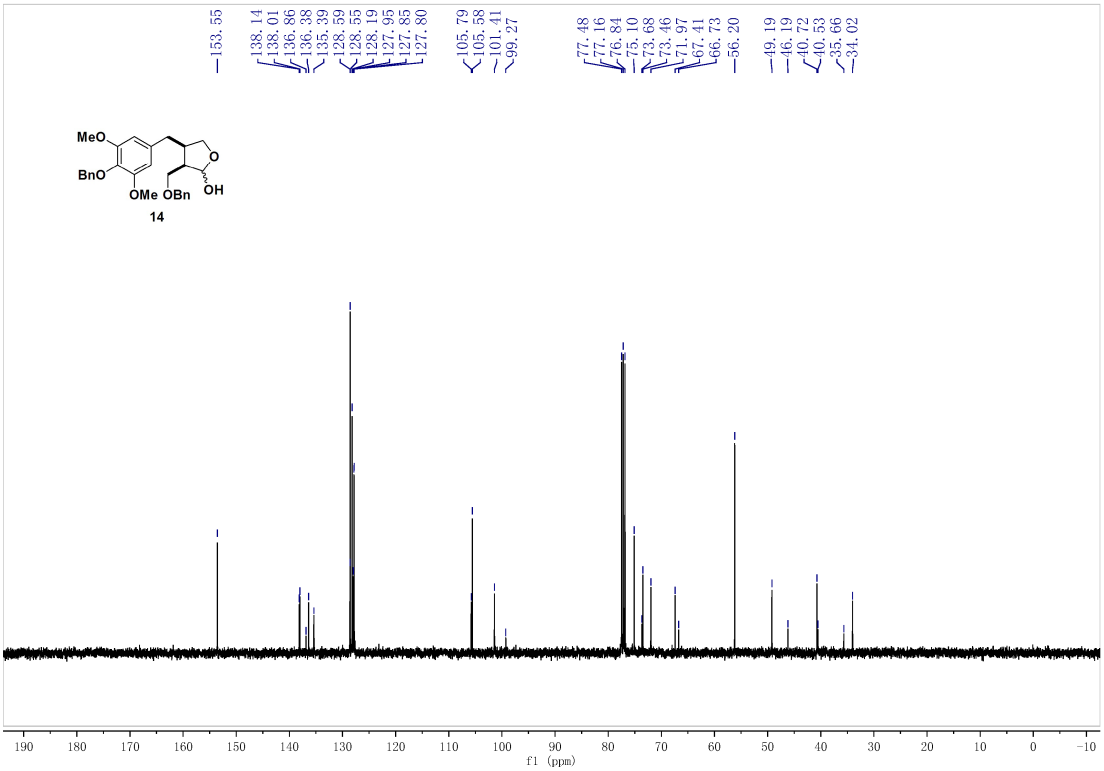
Copy of ^{13}C NMR spectrum of compound **13**



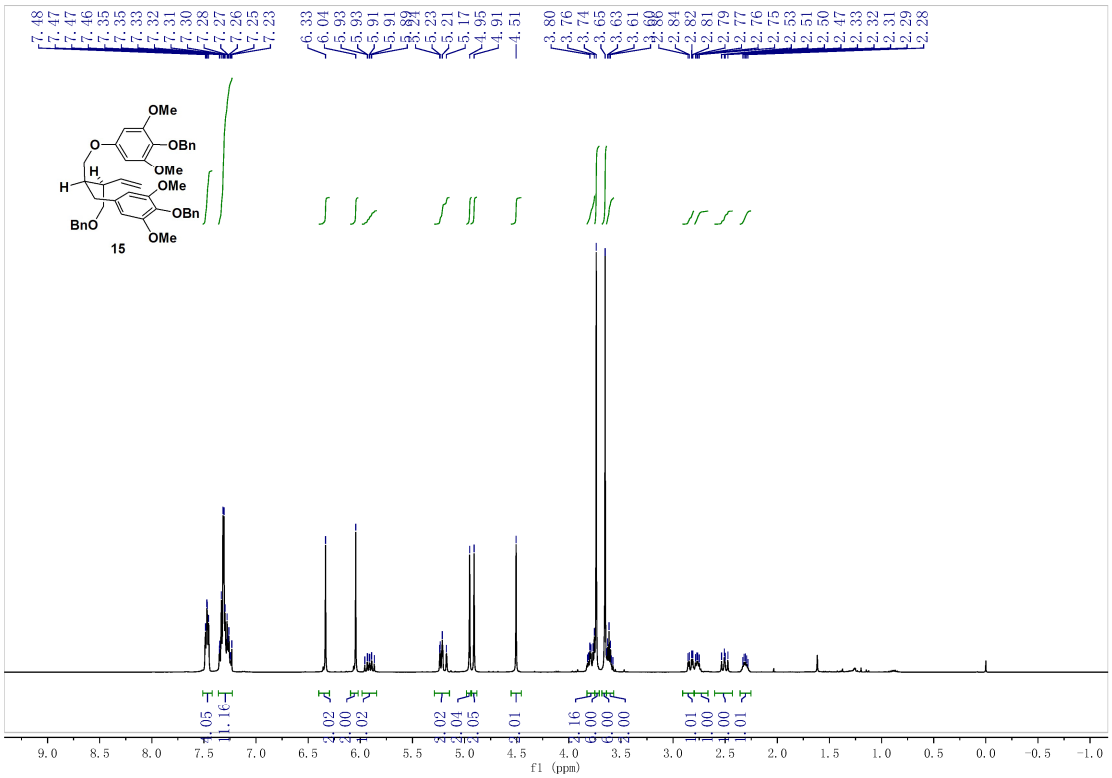
Copy of ^{1}H NMR spectrum of compound **14**



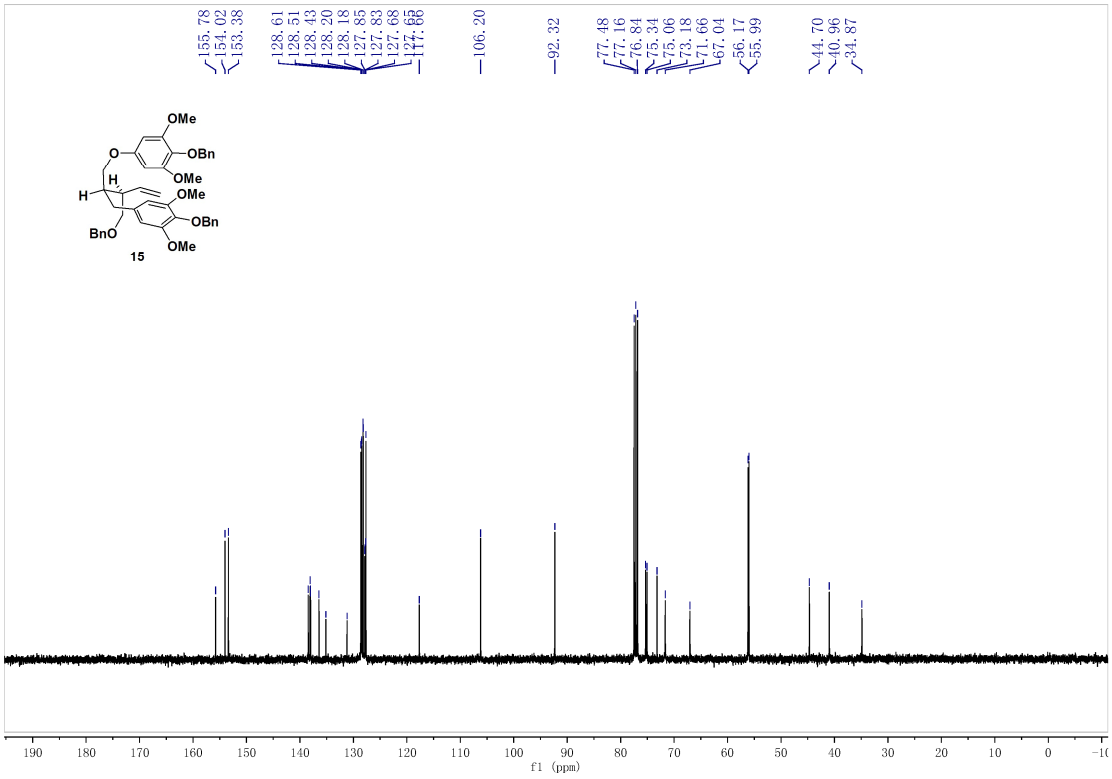
Copy of ^{13}C NMR spectrum of compound **14**



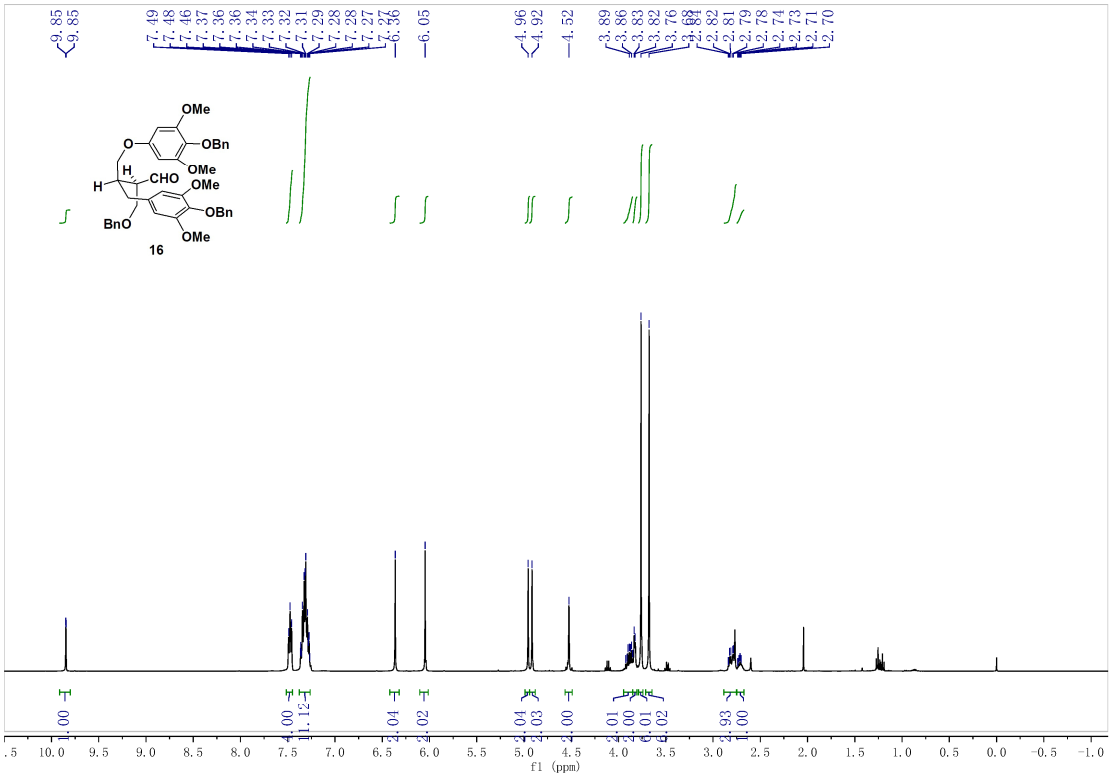
Copy of ^{1}H NMR spectrum of compound **15**



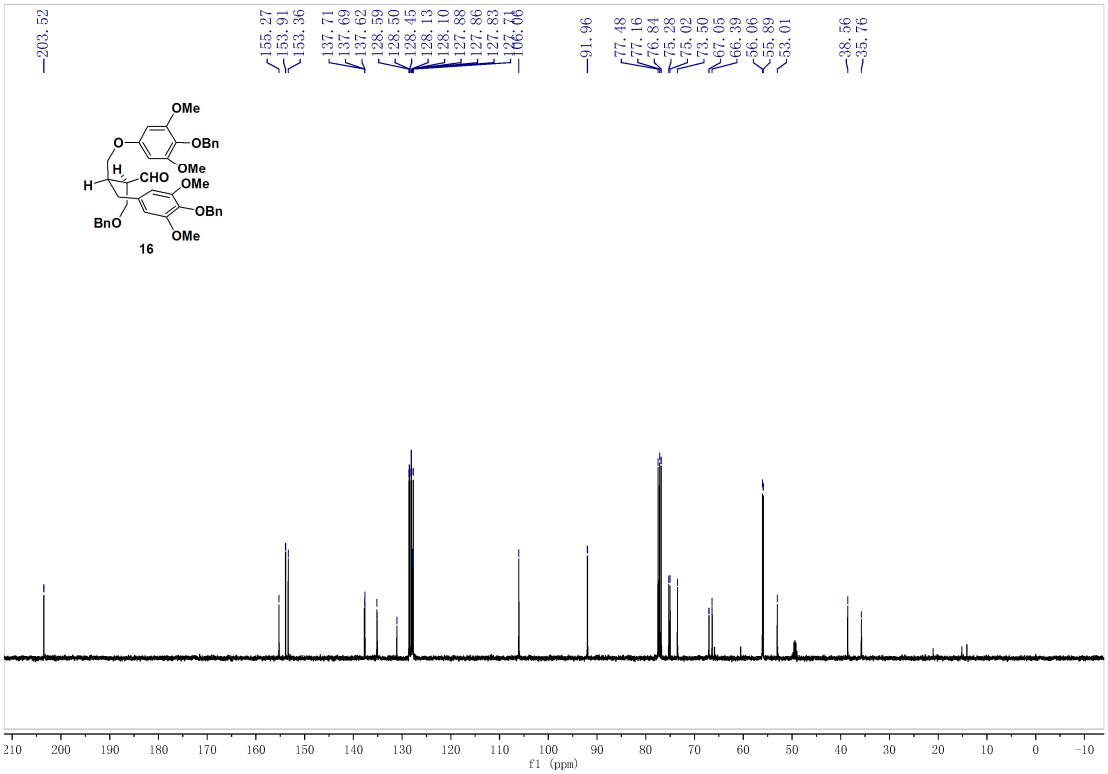
Copy of ^{13}C NMR spectrum of compound **15**



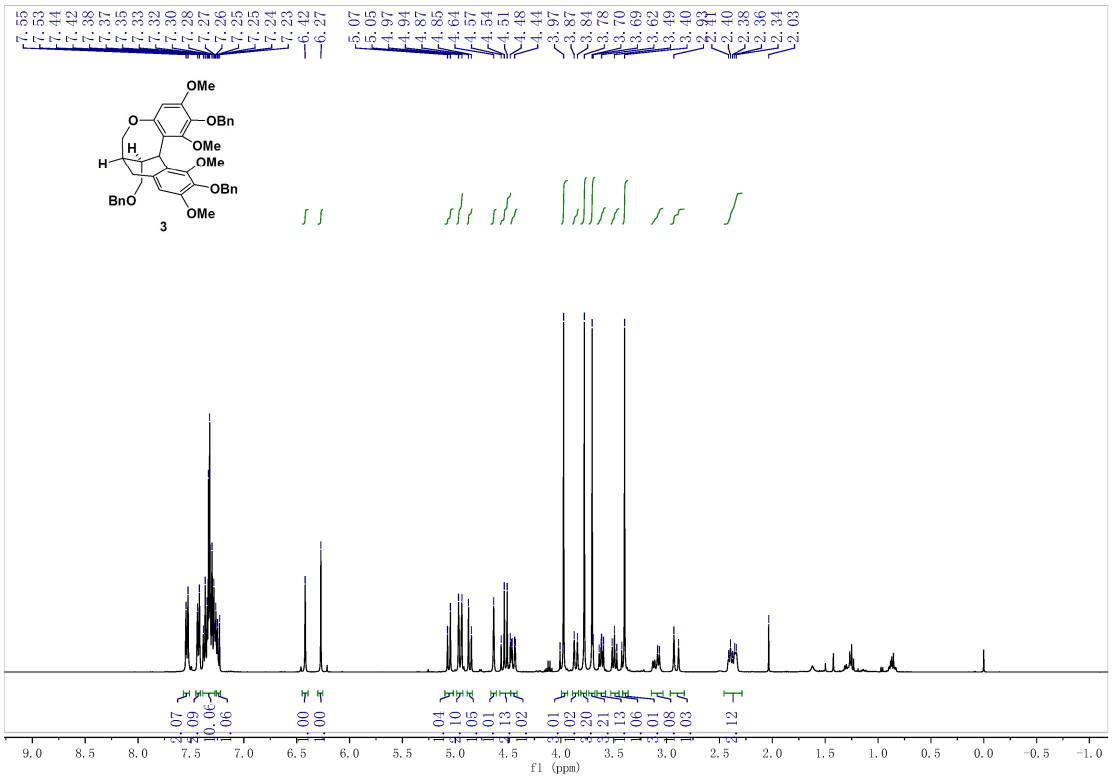
Copy of ^{1}H NMR spectrum of compound **16** (containing small amount of EtOAc and Et_2O)



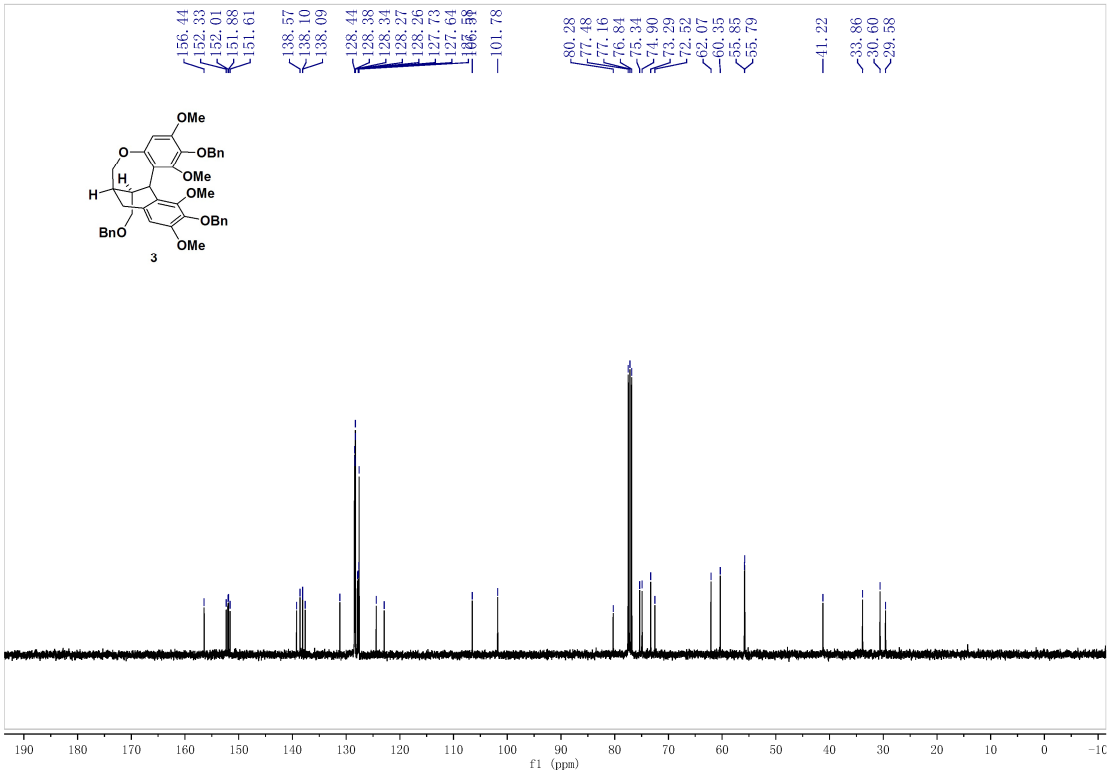
Copy of ^{13}C NMR spectrum of compound **16** (containing small amount of EtOAc and Et_2O)



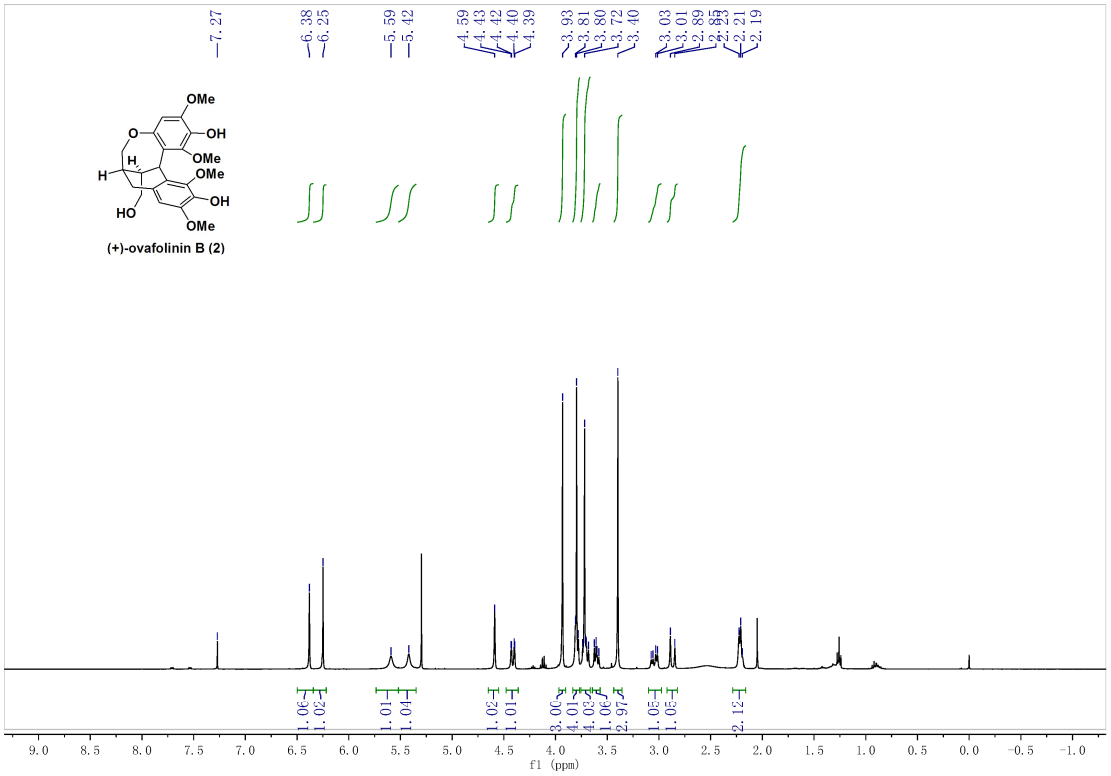
Copy of ^{1}H NMR spectrum of compound **3** (containing small amount of EtOAc)



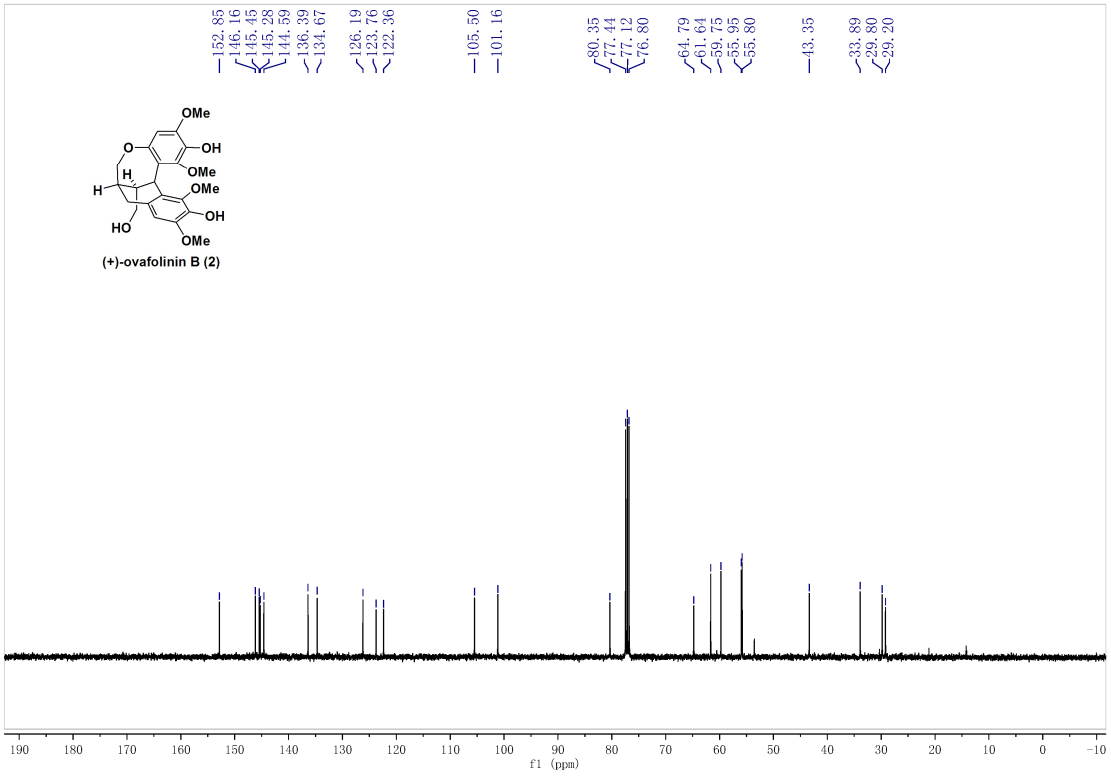
Copy of ^{13}C NMR spectrum of compound **3** (containing small amount of EtOAc)



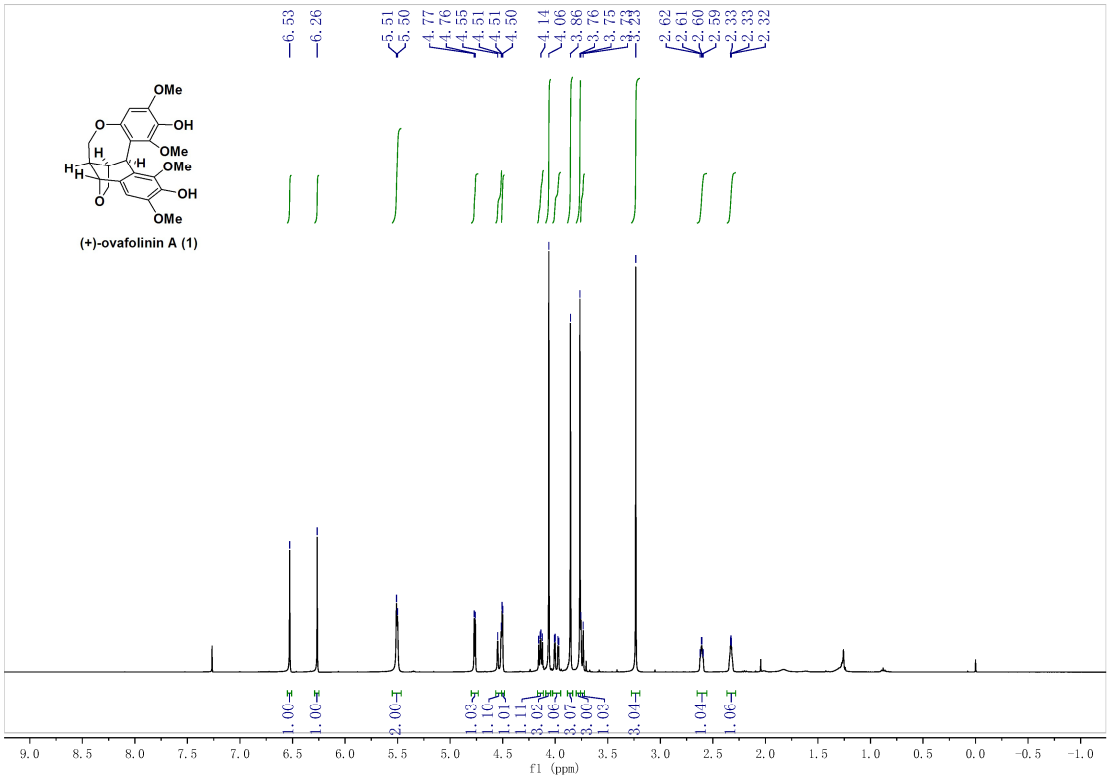
Copy of ^{1}H NMR spectrum of (+)-ovafolinin B (**2**) (containing small amount of EtOAc and CH_2Cl_2)



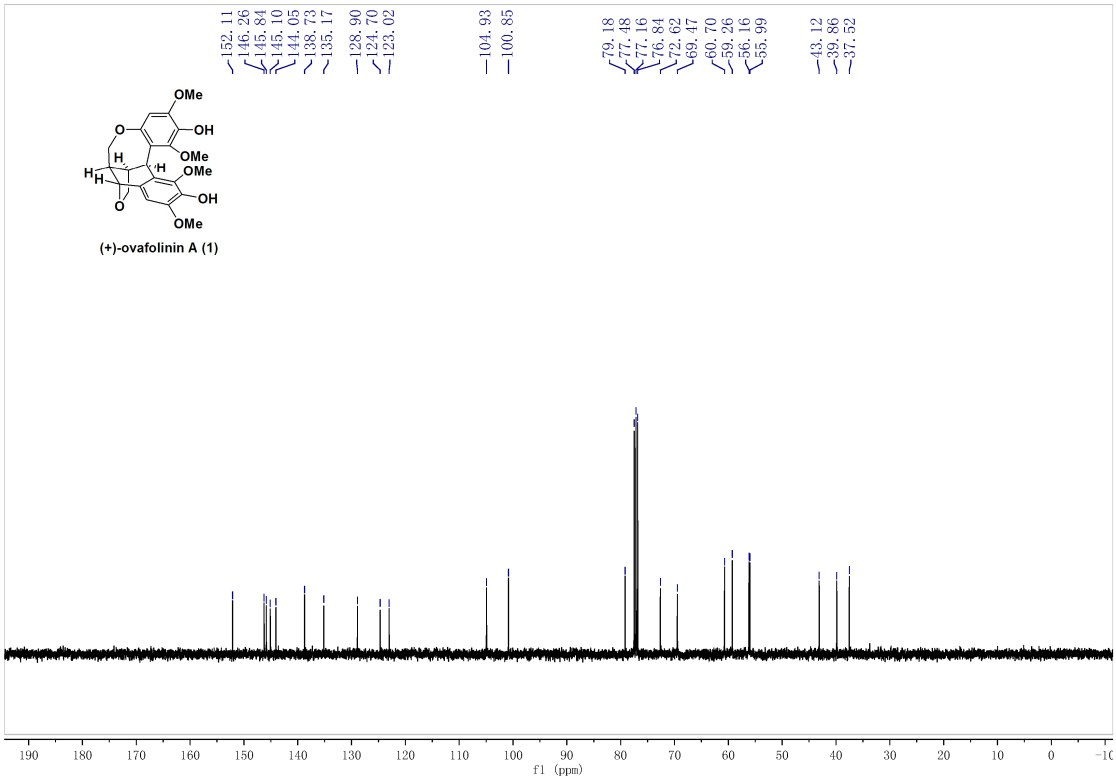
Copy of ^{13}C NMR spectrum of (+)-ovafolinin B (**2**) (containing small amount of EtOAc and CH_2Cl_2)



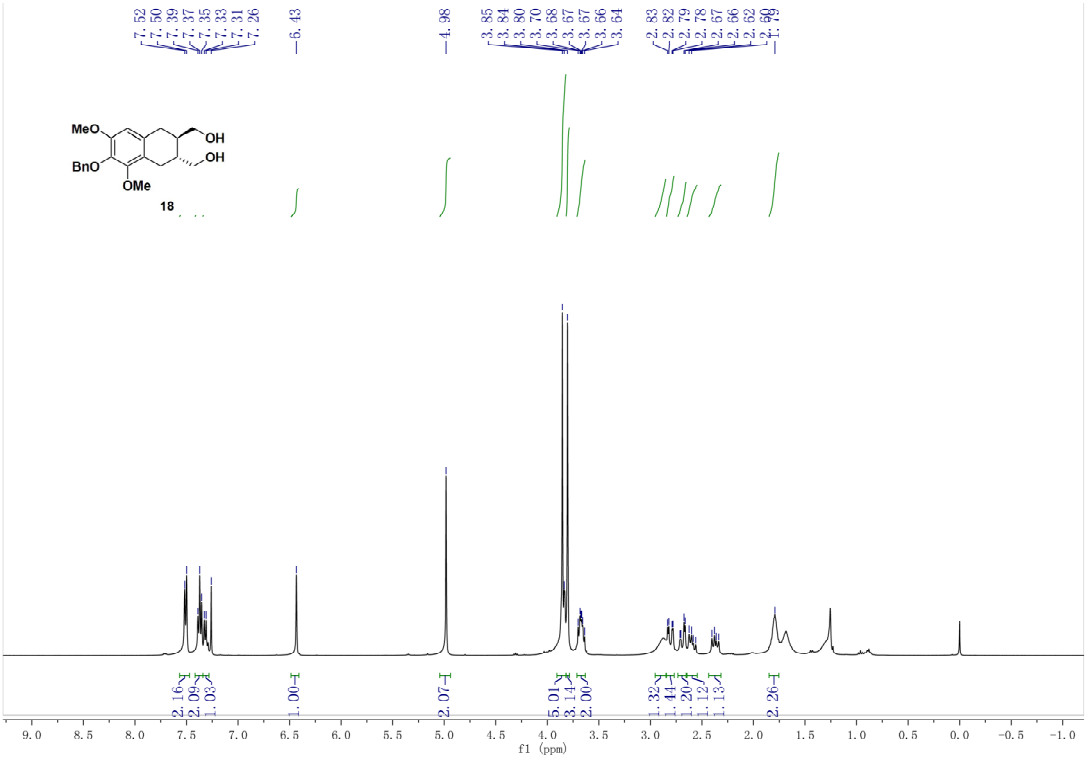
Copy of ^{1}H NMR spectrum of (+)-ovafolinin A (**1**)



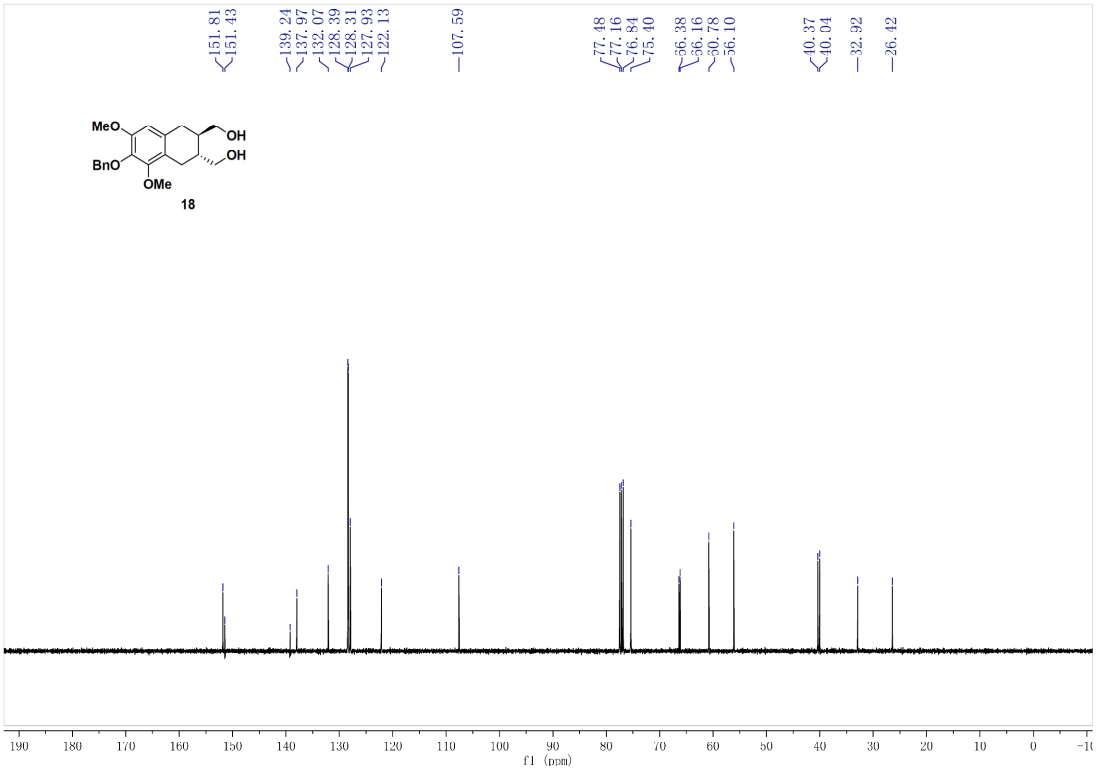
Copy of ^{13}C NMR spectrum of (+)-ovafolinin A (**1**)



Copy of ^{1}H NMR spectrum of compound **18**



Copy of ^{13}C NMR spectrum of compound **18**



Copy of DEPT-135 spectrum of compound **18**